

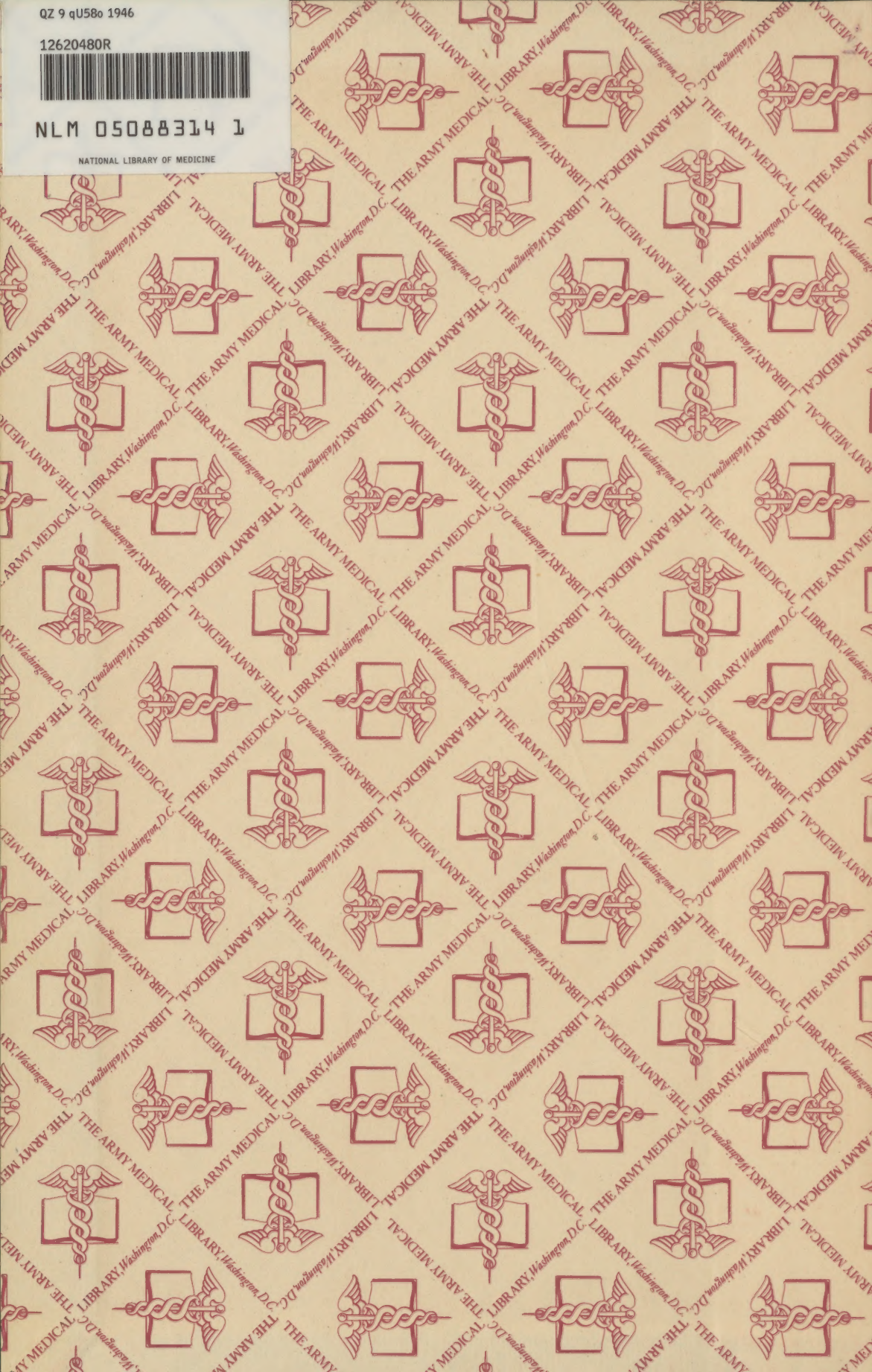
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THE MILITARY SURGEON

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No. 5

ORIGINAL ARTICLES

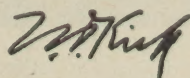
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FOREWORD

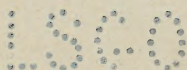
Colonel James E. Ash, Medical Corps, U. S. Army, has just retired after thirty years of distinguished service. He has made signal contributions to the Medical Corps, to the Army, and to the Nation through his guidance of the development and organization of the Army Institute of Pathology. Recognized as the leading pathologist in the Army, his diligence, foresight, professional knowledge, and undeterred devotion to duty have led to the organization of the most extensive service in tissue pathology ever known to the world. Under his leadership the American Registry of Pathology has expanded greatly, and under his supervision the Army Medical Illustration Service was established. The wealth of pathologic and illustrative material brought together at the Army Institute of Pathology has given it a unique position for the study of diseases in the military age group, and for the training of pathologists.

The editors of THE MILITARY SURGEON have issued this special number in honor of Colonel Ash. All the contributions are by members of the Army Institute of Pathology. The papers give a cross-section of the productive investigation carried on at the Institute even under the adverse conditions of heavy war-time routine. They are a tribute of a loyal and devoted staff to their Chief.

The services of the Army Institute of Pathology under the Directorship of Colonel Ash have been of inestimable value to the Medical Department and to the Nation. Colonel Ash richly merits the honor bestowed on him by the publication of this volume.



NORMAN T. KIRK,
MAJOR GENERAL
The Surgeon General



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COL. JAMES E. ASH, M.C., U. S. Army
Director, Army Institute of Pathology

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COLONEL JAMES EARLE ASH

AN APPRECIATION

THE men and women of the Army Institute of Pathology in the exercise of their various talents have contributed this special issue of THE MILITARY SURGEON as a means of honoring and of showing their affectionate regard for the officer who conducted the affairs of the Institute during the years of the lately terminated war.

Colonel Ash who has recently completed his thirtieth year in the medical service of the Army, has devoted the greater number of these years to laboratory work and studies. The University of Pennsylvania in his native city gave him his medical education, and its courses were followed and supplemented by several years of interne service in Philadelphia's hospitals, including the great Blockley institution. By the end of this service he had fixed upon a career of laboratory medicine with his main interest in pathology.

From his interne service he went to the laboratory of the Norristown Hospital for the Insane, a State institution. Three years of service here and he moved on to the Harvard Medical School to work with Professor Howard Thomas Karsner, with whom he had been associated in medical school and in his hospital work in Philadelphia. It was with this background of work in pathology that he entered the Medical Corps of the Army in 1916, with war on in Europe and our military forces massed along the Mexican border. Competent pathologists have always been far too few in the Army to employ them on other than their very special work. It follows then that the list of Colonel Ash's stations is not a long one, but includes nearly all of the permanent General Hospitals that existed prior to our second World War, including the Sternberg hospital in Manila. If we add to these the Army Medical School and the Army Medical Museum the list is about complete. He has had two details to the Museum, the present one still uncompleted, having covered nearly ten years.

Colonel Ash's tenure of office in the Museum has been marked by two major accomplishments. The American Registry of

Pathology, which started its first registry in 1922 was expanded from five to fourteen by Colonel Ash's cooperation with the national medical societies. The registries have the records of 43,000 cases involving unusual pathological material.

The essential function of the Medical Museum, that of pathological diagnosis and research, was long obscured by the name borne by the institution. Through recommendations made by Colonel Ash, the establishment is now the Army Institute of Pathology, which places the emphasis upon the vital work and the museum feature in its proper secondary place. Needless to say Colonel Ash is a master craftsman with all the tools and appliances of the pathologist and a highly competent judge of the material that comes to his hands or that falls under the lens of his microscope.

The widely expanded Institute has been manned during the war by a staff of diligent workers, whose duties have been made the pleasanter by the understanding attitude of its Director. Colonel Ash's quiet supervision is of the quality that obtains a loyal following from those working with him.

It would be expected that a quiet, somewhat introverted person like Colonel Ash should have a liking for music, which can be muted when desired and which requires little or no company for its enjoyment. He is indeed devoted to piano-music, in which he has a talent and always a refuge from boredom.

The burdens of his exacting position have been aggravated for him by an accident to one of his eyes, which has required much treatment during the past year. As this is written, orders for his retirement from active service are awaited.

There is expectation that Colonel Ash, after retirement, will take over the direction of the American Registry of Pathology. His many friends will welcome his continued association with the Institute and wish him a world of contentment in his new work.

J. M. P.

THE ARMY INSTITUTE OF PATHOLOGY DURING WORLD WAR II

By COLONEL BALDUIN LUCKÉ, *Medical Corps*

FOUNDATION. The first World War emphasized the need for a central laboratory of pathology to serve the entire United States Army. During the years between the wars such a laboratory was organized as a department of the Army Medical Museum, which itself had been founded during the War between the States. In the course of years, and particularly with the expansion of the Army during the period of mobilization and war, the department of pathology assumed much greater medicomilitary importance than the parent organization. The enlarged scope of its activities and the frequent and serious misunderstandings of its function because of the name, Army Medical Museum, led the Surgeon General to approve, in 1943, a new designation, "The Army Institute of Pathology"; the title of the commanding officer was changed from Curator to Director. Thus, both the Army Institute of Pathology and the Army Medical Museum trace their origins to times of national emergency.

Organization and Function. The Army Institute of Pathology operates under the direct control of the Surgeon General, in conformity with Army Regulations (AR 40-410). It comprises four departments which are administratively co-ordinated: The Department of Pathology, The Army Medical Illustration Service, The American Registry of Pathology, and the Army Medical Museum. The principal functions of the Institute may be summarized as follows: (1) It is the central laboratory of pathology for the United States Army. (2) It furnishes a consultation service for the diagnosis of pathologic tissue, and it acts as the chief reviewing authority on the diagnosis of pathologic material for all Army installations. (3) It provides instruction in pathologic anatomy to medical, dental and veterinary officers. (4) It conducts research in the pathology of diseases which have medicomilitary importance. (5)

It is the headquarters of the Army Illustration Service. (6) It houses and acts as custodian of the American Registry of Pathology, and (7) It maintains the Army Medical Museum for the instruction of medical department personnel and the education of the public.

This enumeration does not exhaust the list of activities but it suffices to indicate the broad plan on which the Army Institute of Pathology was developed.

A brief discussion may now be given of the aims and the work of the several departments, excepting the American Registry of Pathology an account of which may be found elsewhere in this issue.

Department of Pathology. Three essential functions, diagnosis, teaching, and research, are performed by the Department of Pathology. Here are referred for diagnosis or review of diagnosis, and for permanent file, the pertinent records and the tissues from *all* important surgical operations (such as tumors) and from *all* postmortem examinations on military personnel of the entire Army. Some of this material is sent directly to the Institute, but most of it first passes through other laboratories known as "histopathologic centers." As organized for wartime, one or more of these centers were located in each of the nine service commands of the Zone of the Interior, and others throughout the various Theaters of War. Similar centers and the laboratories of a number of general hospitals function on this plan, which proved so efficient in the active phase of war. They make immediate examinations, "screen out" relatively unimportant material, and forward to the Institute such data and material as may have either scientific or administrative significance, from surgical cases and all autopsies. Here the material is re-examined, and the submitting station is notified of the opinion of the staff pathologists. Air mail and radiograms enable military installations, no matter where they are located, to make immediate use of the facilities of the

institute. This service protects military personnel as well as the Government against possible errors in diagnosis, and aids surgeons, internists and other medical officers in their work by facilitating the diagnosis, treatment, and prevention of disease. Moreover the centralization in one laboratory makes it possible for the Office of the Surgeon General to obtain promptly accurate information on the causes of death, the diagnosis of operative cases, and the regional trend of disease.

The volume of material received at the Institute is considerable. During 1945 the records and tissues from 18,895 postmortem examinations and from 20,539 selected surgical operations were submitted, the latter presenting mainly diagnostic problems. The handling of such an amount is an administrative and technical problem. Each "case" is given an accession number under which is filed all pertinent material including written records, specimens, blocks, slides and photographs. Many tissues are prepared for microscopic examination by special methods. All records are analyzed; all diagnoses cross-indexed for ready availability.

The steady growth of the work of the Institute from the beginning of the first, to the end of the second, World War is shown in Figure 1. The polygons represent the cumulative increase in the number of accessions. The curve in the insert shows the number of "cases" studied during World War II; the dotted line at the terminal of the curve, the probable number of accessions for the next two years. This estimate is based on the expectation that the decrease in the size of the Army will be more than balanced by the increase in the Veterans' Administration.

The second function of the Department of Pathology, teaching, was carried on during the War along two lines: Medical officers from key laboratories were placed on temporary duty at the Institute to gain first hand information concerning its facilities. A valuable part of the training was attendance at the daily staff conference, where important current cases were reviewed by members of the staff. Microscopic slides were projected and the gross

specimens and x-ray plates were shown when pertinent. The presentations were brief but to the point, and the discussion, in which everybody participated, free and lively.

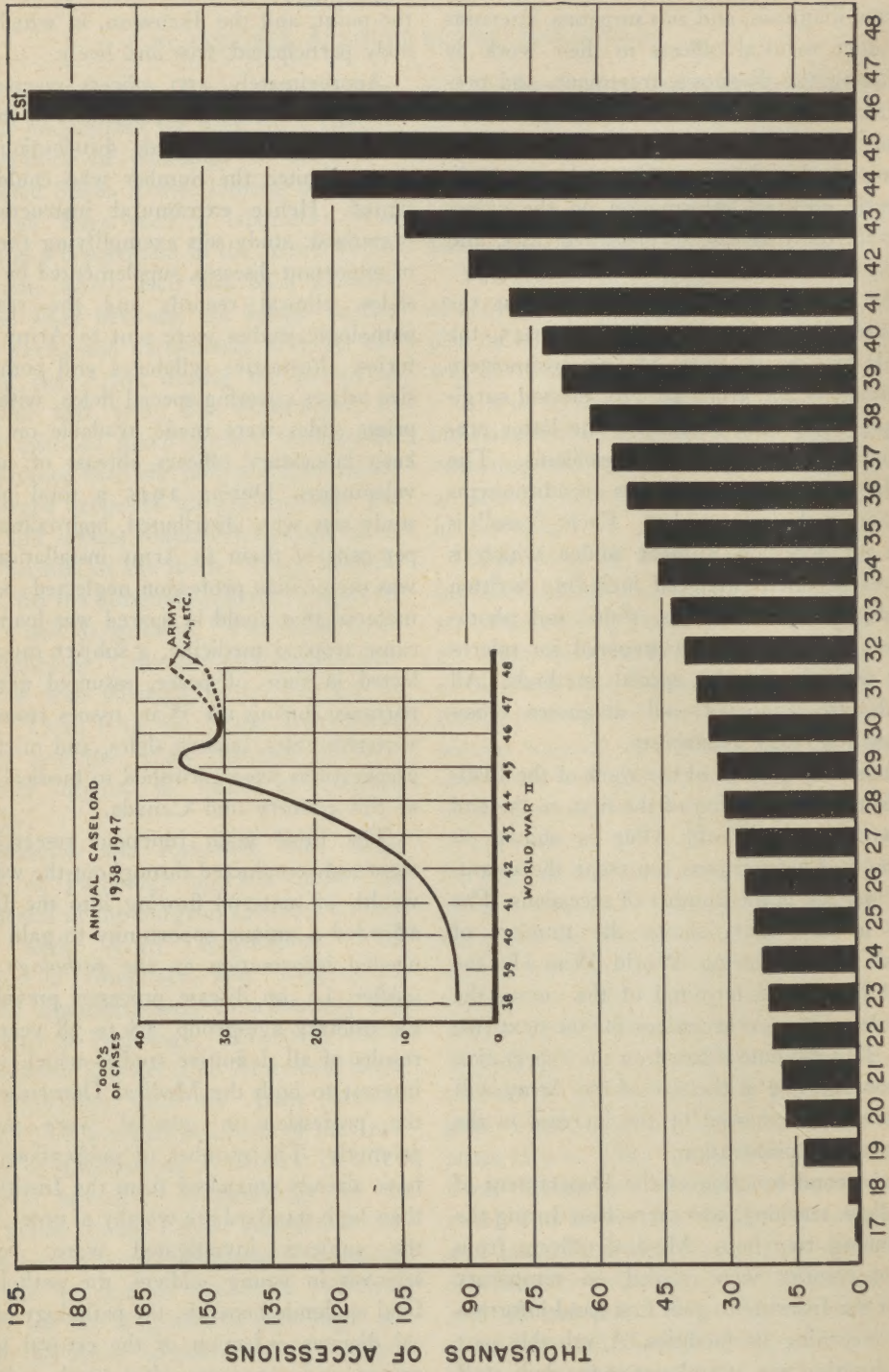
Approximately 150 officers received such training; the crowded conditions at the Institute and the world wide distribution of the Army limited the number who could be assigned. Hence extramural instruction was organized: study sets exemplifying the lesions of important diseases, supplemented by lantern slides, clinical records and the results of pathologic studies were sent to Army laboratories. Illustrative syllabuses and comprehensive atlases covering special fields, with appropriate slides were made available on loan to keep laboratory officers abreast of new developments. During 1945 a total of 1669 study sets were distributed, approximately 90 per cent of them to Army installations. Nor was the civilian profession neglected; all study material that could be spared was loaned. Because tropical medicine, a subject much neglected in time of peace, assumed great importance during the War, tissues from representative cases, lantern slides, and microscopic preparations were furnished to medical schools of this country and Canada.

The third main function, research, was vigorously conducted throughout the war. The wealth of material flowing into the Institute afforded a unique opportunity to gain greatly needed information on *the pathology of the soldier*, i.e. on disease processes prevalent in the military age-group, 18 to 38 years. The results of all definitive studies which were of interest to both the Medical Department and the profession in general were published promptly. The number of publications which have already emanated from the Institute and their high standard are worthy of note. Among the subjects investigated were: coronary sclerosis in young soldiers, the pathology of fatal epidemic hepatitis, the pathology of tropical diseases, infection of the central nervous system and meninges after tooth extraction, pathology of trench foot, comparative pathology of scrub typhus and other rickettsial disease, peripheral nerve injuries, fat embolism,

GROWTH OF ARMY INSTITUTE OF PATHOLOGY

1917 - 1946

CUMULATIVE INCREASE IN CASE ACCESSIONS



TOTAL NUMBER OF ACCESSIONS AT EACH YEAR - END

FIG. I

gynecomastia, teratoma of the anterior mediastinum, and odontogenic tumors. The papers in this issue of the *MILITARY SURGEON* are other examples of studies which were started during the War. These studies and others will form the basis for the Volume on Pathology in the *Medical History of World War II*.

Staff. The Institute was fortunate throughout the War to have as its commanding officer a man of high professional attainments, who was liked and trusted by everyone, who inspired loyal devotion to duty, and who, without seeming effort, was able to weld the staff into a harmonious working unit: Colonel J. E. Ash. Perhaps no man knows the Institute, its early trials and its ultimate success as does he, for he served there from March 1929 to September 1931, and again from February 1937 until his recent retirement. Few medical officers have as extensive an acquaintance or have kept in as close touch with civilian pathologists throughout the country. The Institute owes much to these attributes.

Soon after the beginning of hostilities Colonel Ash brought together a professional staff which was selected on the basis of specialized knowledge and competence in the various branches of pathology. Thus it was possible for the group to render expert opinion on difficult or controversial diagnostic problems and to conduct essential teaching and research. The staff was never large; it averaged fewer than fourteen pathologists, but these were hand-picked and they remained on duty for the major part of the war. Eight were stationed at the Institute for more than three years, four for more than two.

An important aid to these officers were the Resident Consultants. A total of seventeen distinguished civilian pathologists were invited to act as Consultants to the Staff, and to undertake, or to collaborate in, certain investigations. Most of them spent approximately one month in residence, but several remained for as long as three months or returned for additional terms of duty. The Consultants were a great stimulus to the staff. Their interest did not flag when they returned to their own

laboratories; most of them continued to pursue investigations begun at the Institute. Twelve of the consultants have made, or have in progress, valuable contributions to the research program, two examples of which are printed in this volume.

Not the least service was rendered by the detachment of approximately thirty enlisted men and WACS, and about twice that number of civil service personnel. Without their technical and clerical help the Institute would not have been able to function.

The Army Medical Illustration Service. The Photographic Laboratory, established over eighty years ago, and the Museum and Medical Arts Service, organized during the War, make up the Army Medical Illustration Service. The former has long been distinguished for the excellence of its photomicrography. Its wartime tasks were heavy. For example, during 1945, the photographic laboratory made, in round numbers, 10,000 negatives, over 50,000 prints and enlargements, over 10,000 lantern slides in color and 5,000 more in black and white, over 30,000 photostats, and over one million offset prints.

The Museum and Medical Arts Service (recently reorganized under the name of Medical Mobile Photographic Units) had its headquarters at the Institute and nine units in overseas theaters of operation. The units consisted of one officer and seven enlisted men, all of whom were well trained medical artists or photographers. Through their work the medical department was furnished with moving and still pictures of nearly every phase of medical activity in combat areas; these illustrations were not only invaluable for training purposes, but they constitute a record of lasting historical value.

This organization was also charged with the supervision of medical photography in the Zone of the Interior. To it were submitted all photographs and moving pictures taken in Army hospitals in this country. During 1945 it received for review and file over 75,000 photographs and nearly 100,000 feet of moving picture film.

Another contribution of the MAMAs, as

they were called, was the production of plastic models representing different kinds of wounds and of sets of posters illustrating first-aid procedure. Many thousands of such models and posters were distributed to Army installations for purposes of instruction. Both the Photographic Laboratory and the Museum and Medical Arts Service were headed by able men of vision and devotion to the Army. They made the Institute the headquarters of medical arts for the Medical Department.

Army Medical Museum. The exigencies of war made it necessary to store large portions of the collections, so that the space could be used for laboratories and offices. The main hall, however, was kept open, for even with the restrictions in travel, the Museum drew as many as 200,000 visitors annually, indicating the interest of the public in medical exhibits.

Future. This brief sketch would be incomplete without mentioning plans for the future.

The Army Institute of Pathology is unique: it is the only institution of its kind in the world. It has amply proved its worth to the Army and to the Nation. The present quarters of the Institute are unsuitable and inadequate. Recognizing these facts The Surgeon General immediately after cessation of hostilities requested Colonel Ash and the Committee on Pathology of the National Research Council to submit recommendations "for the most advantageous use of the facilities of the Army Institute of Pathology, both for the Army Medical Department and for the medical profession as a whole." Meetings of this Committee with Colonel Ash and his staff led to plans for a new Institute which have been approved by The Surgeon General and the War Department. Thus we may look forward to a new Army Institute of Pathology, which, while retaining its special traditions, will be enabled to render even greater service in a wider field.

THE AMERICAN REGISTRY OF PATHOLOGY AND ITS RELATION TO THE ARMY INSTITUTE OF PATHOLOGY

By HOWARD T. KARSNER, M.D., *Resident Consultant, Army Institute of Pathology*

COLLECTION for the sake of mere possession is as futile in medicine as in any other field. In cultural spheres, the art museum serves as a source of education to the public, of stimulus to artists, and of research in history both special and general, and the library has much the same purposes. In science, however, although the objectives are the same, the emphasis often differs in that research occupies the foremost position, even though education and stimulation are prominent aims.

A museum of pathology may be principally educational, but it is not fully utilized unless the opportunity for research is seized. A registry of pathology or of any of its special branches differs from a museum in several respects. In the registry, display of specimens is not a principal function; study of the material is both the primary and principal objective.

Whereas records of the source of museum specimens is important, in the registry they are essential. In the museum, "follow-up" adds greatly to the value of the material, but in the registry the purpose is defeated if "follow-up" is not pursued assiduously. The museum may be conducted by a curator not necessarily an expert in the field covered, but the registry requires highly trained, experienced, competent scientific personnel at its head and in many parts of its organization. A museum may be collected locally, but a registry must have contributions from widely dispersed sources.

A registry is usually established because of the direct interest of a comparatively small group of inspired guiding spirits. The location of the registry may be determined by the institutional situation of an individual or small group. However, to be most effective, the

registry must be at least national in scope and often, if it is placed in a local institution, various factors may operate so that collection may not be adequate. As a consequence of these elements, the Army Institute of Pathology, situated in the capital city of this country, has been especially favored. This Institute is unique in the world. Nowhere else has there ever been a concentration of pathological specimens that is comparable. Nowhere else is the pathology of the entire Army of a great country so concentrated. Nowhere else have the civilian pathologists and other interested physicians taken such a great part in organization and operation. Nowhere else has there been, as continues to be true, such a close scientific liaison between medical officer and civilian doctor.

It is only natural that when the American Academy of Ophthalmology and Otolaryngology decided to form a registry it should turn to the Army Medical Museum. The Curator, George R. Callender, now Brigadier General, M.C., opened the Registry of Ophthalmic Pathology in 1922. At the end of 1945 there was a total of 19,385 accessions in this registry alone, a material which has led to numerous important studies, especially of melanotic tumors of the eye. In 1925, a Registry of Tumors of the Lymphatic System was established at the behest of the American Association of Pathologists and Bacteriologists and now has 2,638 accessions. In 1927, the American Urological Association sponsored a Registry of Urologic Pathology, which has a total of 5,940 accessions of which over 5,000 refer to tumors of the bladder. Beginning in 1933, and continuing through 1945, 11 other registries have been formed, including Dental and Oral Pathology, Otolaryngological Pathology, General Tumors, Dermal Pathology, Renal Tumors, Thoracic Tumors, Neuropathology, Orthopedic Pathology, Prostatic Tumors, Veterinary Pathology, and Gerontology, all sponsored by special national societies. Naturally, the collected material varies in amount with the registry but the total num-

ber of accessions has reached 43,442.

A movement once started may grow of its own momentum. The history of the registries, however, shows that in the first half of the period between 1922 and 1946, 4 registries were started and that in the latter half, 10 were organized, with more to come in the near future. The impetus given by Gen. Callender was undoubtedly of great significance. The subsequent growth, however, was due almost entirely to the industry and interest of James Earle Ash, now Colonel, M.C. Here was a man trained at Pennsylvania, Harvard and Vienna, one who had early decided that his career was to be devoted to pathology, one who throughout his Army life gave selfless effort to the development of Army laboratories. There could be no question as to his competence in his field. With this exceptional background of general pathology, he could turn his attention to special fields with every assurance that his work would be broadly based and expert. Through his devotion to the registries he has brought to the special societies a wealth of analysis and information which cannot be equalled. Civilian medicine has profited enormously by the skillful study of specimens and cases. The material was also of great value in the training of Medical Officers, who during World War II, conducted laboratories in the widely dispersed theaters of operation. Colonel Ash's modesty of demeanor could not hide his merit, his sympathy, his competence, or his deep interest in the projects. These attributes, coupled with his fine character, straightforwardness and integrity had much to do with the confidence reposed in him by the members of the sponsoring societies. Medicine and the military profession as a whole owe an eternal debt of gratitude to Colonel James Earle Ash as physician, pathologist, medical officer, Curator of the Army Medical Museum and Director of the Army Institute of Pathology, for many reasons, not the least of which is his consecration to the origin, development and operation of the American Registry of Pathology.

THE REGISTRY OF DENTAL AND ORAL PATHOLOGY AT THE ARMY INSTITUTE OF PATHOLOGY

IN 1933, when the American Dental Association authorized the establishment of the Registry of Dental and Oral Pathology at the Army Institute of Pathology, the first attempt was made by the dental profession toward establishing a central laboratory of oral pathology. Before this time there was but little specialization in dental pathology, and the contact between dental pathologists and the medical profession in general was slight. In an effort to better this situation, the American Dental Association instituted the Registry program, which was designed primarily to demonstrate the importance of dental and oral pathology and to further the relationship between medicine and dentistry. It was essential to the success of the Registry that it have the support of the practitioners of dentistry, the encouragement of the Director of the Institute, and the diligent and active efforts of the Registry Committee of the Association. Fortunately all of these requirements were met as the program developed. Progress was slow but continuous, the guiding spirit during the critical periods being Colonel James E. Ash, the Director of the Army Institute of Pathology from 1929 to 1931 and 1937 to 1946. Because of his constant support the Registry was able to expand to a point where its importance to the progress of dentistry became clearly apparent to the profession at large.

Some of the more important facilities, such as the biopsy service, the loan sets and the atlas were produced at the suggestion of Colonel Ash. His contributions have been continuous, not only as plans but also as the work that made them a reality. The guidance of one so outstanding in the field of pathology has been essential in bringing the Registry of Dental and Oral Pathology to the recognized position it holds today. Its files now contain over 6,000 selected cases from which teaching material has been prepared for dental schools, study clubs, and practitioners. The value of this Registry should not only be measured in terms

of services rendered and material collected, but particularly in the changed point of view of the practicing dentist toward pathology as an adjunct in improved care of his patient.

We who have been interested in the growth of the Registry are convinced that it would not occupy its present position except for the support it received from the medical profession and the Army Medical Department. It was through the efforts of Colonel Ash that this support was forthcoming, particularly during the critical period when the Registry was struggling to attain the status enjoyed by other more established registries. His diligent efforts to procure adequately trained personnel, his insistence upon equal representation for the dental profession, and his foresight in general has insured the attainment of the desired goal.

The dental profession owes a debt of gratitude to Colonel Ash for his efforts in its behalf. Only those who have been actively associated with the Registry during its period of growth can realize how much has depended on this one individual, how many significant advances have been made at his suggestion and through his intercession. The most recent of them have been the establishment of a Fellowship in Dental and Oral Pathology at the Army Institute of Pathology and the organization of the American Academy of Oral Pathology.

Even though Colonel Ash has come to the time when he will relinquish the directorship of the Institute, because of retirement from the Regular Army, it is the hope of every member of the American Dental Association that he will remain in close touch with the organization which owes so much to his enthusiasm and leadership.

HENRY A. SWANSON,
Chairman, Committee on National
Museum and Dental Registry
American Dental Association

JOSEPH L. BERNIER,
Secretary

LOWER NEPHRON NEPHROSIS*

(THE RENAL LESIONS OF THE CRUSH SYNDROME, OF BURNS, TRANSFUSIONS, AND OTHER CONDITIONS AFFECTING THE LOWER SEGMENTS OF THE NEPHRONS)

By COLONEL BALDUIN LUCKÉ, *Medical Corps*
(From the Army Institute of Pathology, Washington 25, D.C.)

(With sixteen illustrations)

INTRODUCTION

DURING the early stages of the war, British pathologists,^{13-17,30} drew attention to distinctive lesions of the kidney found in fatal cases of the crush syndrome, a condition characterized by renal insufficiency following crushing injury to muscle. The syndrome was not new; it had been described during the first World War, but in the interim had been all but forgotten.⁶³ Its rediscovery led to intensive study, and soon it became clear that the renal changes are not specific for the crush syndrome. Similar or identical lesions have been observed in a variety of conditions: after any severe trauma to muscle,^{9,14,27,46,71} nontraumatic muscular ischemia,^{12,18,43} burns,^{46,53} transfusion with incompatible blood,^{3,25,26,28,40} and heat stroke;⁵⁸ also in blackwater fever,^{40,56} toxemias of pregnancy and uteroplacental damage,^{37,72,90} alkalosis,⁵⁵ sulfonamide intoxication,^{41,42,52} and poisoning with certain vegetable and chemical agents.^{12,40,48} These conditions all have features in common. In each the initiating factor consists in destruction of tissue or of blood. Clinically, shock is usually an early manifestation, followed by renal insufficiency which develops according to a definite pattern. In all, the renal lesion is essentially the same: degeneration, often necrosis, limited to the distal segments of the tubules, with brown casts of some heme compound in the lower nephrons and the collecting tubules.

We may, therefore, regard the kidney lesion in the crush syndrome, in transfusion nephrosis, in burns and the other conditions mentioned as unique and regularly attended by characteristic functional disturbances. There-

fore, it is appropriate to designate all cases exhibiting these renal disturbances, no matter what their etiologic background, by a single term. Because of the prominence of the heme casts and the primarily degenerative nature of the lesions, the collective term "hemoglobinuric nephrosis" has been widely used. Even though the heme casts are a prominent feature, the location of the lesions is so characteristic and unique, that the term "lower nephron nephrosis" seems more descriptive and has been adopted.

Lower nephron nephrosis has been the most frequent form of fatal kidney disorder encountered among military personnel during the war. For example, Mallory⁵⁹ observed it in 10 per cent of the first thousand autopsies reviewed by him in the Mediterranean Theater; among 427 battle casualties dying in hospital, the incidence was 18.6 per cent. Similarly, Angevine and Harman² found these renal lesions in 15.2 per cent of 1065 cases in which death resulted from battle wounds.

MATERIAL

This investigation is based upon 538 fatal cases, the records and material of which were received at the Army Institute of Pathology during the war (179 additional cases were excluded because pertinent data were incomplete).

The conditions in which the characteristic renal lesion was observed are given in Table I. Eleven groups are represented, namely: battle wounds, crushing injuries, abdominal operations, burns, blood-transfusion reaction, sulfonamide intoxication, heat stroke, falciparum malaria (black-water fever), poisoning due to a variety of agents, hemolytic anemia, and a miscellaneous group containing such unrelated conditions as uteroplacental damage, acute

* This communication is based on lectures delivered at the Army Institute of Pathology.

TABLE I

ETIOLOGIC FACTORS IN 538 FATAL CASES HAVING THE CHARACTERISTIC RENAL
 LESIONS OF LOWER NEPHRON NEPHROSIS

(Under Most of the Groups Listed Are Given the Number of Cases which Received Transfusions of Blood, Sulfonamides, or Both, as Therapeutic Measures)

<i>Battle Wounds</i> (Gunshot, mine explosion, blast injury, severance of large blood vessel, etc.)	221
Transfusion and sulfonamide treatment	126
Transfusion	79
Sulfonamide	11
No transfusion or sulfonamide	5
<i>Crushing Injuries</i>	46
Transfusion and sulfonamide treatment	21
Transfusion	16
Sulfonamide	4
No transfusion or sulfonamide	5
<i>Abdominal Operations</i> (Carcinoma of colon, stomach, pancreas, etc. ruptured ulcer of duodenum or stomach; ruptured appendix, etc.)	36
Transfusion and sulfonamide treatment	18
Transfusion	11
Sulfonamide	3
No transfusion or sulfonamide	4
<i>Burns</i>	48
Transfusion and sulfonamide treatment	19
Transfusion	12
Sulfonamide	0
No transfusion or sulfonamide	17
<i>Blood Transfusion Reaction</i> (In cases of trauma, poisoning, infections, etc.)	45
<i>Sulfonamide Intoxication</i> (In cases of meningitis, pneumonia, other nontraumatic infections, infections associated with trauma, etc.)	47
<i>Heat Stroke</i>	19
Transfusion and sulfonamide treatment	1
Transfusion	10
No transfusion	8
<i>Malaria (Falciparum); Blackwater Fever</i>	14
Transfusion and sulfonamide	0
Transfusion	6
Sulfonamide	2
No transfusion or sulfonamide	6
<i>Poisons</i> (Arsenicals, 3; carbon tetrachloride, 3; alkali, 2; carbon monoxide, 1; alcohol (adulterated), 2; isopropyl alcohol, 1; phenol, 4; photodeveloper, 2; mussel, 1; mushroom, 1)	20
<i>Hemolytic Anemia</i> (Etiology undetermined)	4
<i>Miscellaneous</i> (Uteroplacental damage, eclampsia, acute pancreatitis, "shock" from various causes, etc.)	38

pancreatitis, and rickettsial disease. The significance of these conditions as the sole or major etiologic factor in the production of the renal lesions may be questioned; the table shows that in the majority of cases in most of the groups, blood-transfusion, sulfonamides, or both were employed as therapeutic measures. Since transfusion with mismatched blood and sulfonamide intoxication may themselves induce the lesions under discussion, it is not possible to decide in every instance if the

treatment was not in itself a factor in the production of the kidney changes. An effort has been made, however, to separate all cases with frank transfusion reaction or with evidence of sulfonamide intoxication; in these, the treatment has been considered of dominant etiologic significance.

Assuming that in every case the condition listed had a major causal relation to the fatal syndrome, it is seen that in more than one-half (57 per cent) the origin was traumatic: a

battle wound, a crushing injury, or a surgical operation. In the majority of the remaining cases there was probably intravascular hemolysis. Occasionally trauma was relatively slight or massive hemolysis was not evident. In such cases severe and prolonged shock seemed to be the outstanding etiologic factor.

CLINICAL MANIFESTATIONS

The salient feature of lower nephron nephrosis, common to all the conditions cited, is rapidly progressing renal insufficiency. A number of investigators have published excellent clinical descriptions of the syndrome as it develops: after crushing injury,^{9,13-15} after non-crushing injury,^{27,45,50,71} in nontraumatic forms of myoglobinuria,^{12,18,43,64} after burns,^{46,53} after incompatible transfusions of blood,²⁶ in blackwater fever,^{40,56,86} in favism,⁴⁰ in sulfonamide intoxication,⁵² in heat stroke,⁵⁸ and after uteroplacental damage.^{72,90} This list of references is fragmentary but it may serve as a guide to further reading. In all these conditions the clinical course and the laboratory findings are essentially similar. Basing our observations on the fatal cases studied at the Army Institute of Pathology, we shall consider, in order: certain complications commonly associated with the precipitating condition; the urinary manifestations; the disturbances of the chemical composition of the blood; the development of hypertension; of edema; and of uremia; and finally, the duration of the disease. To illustrate the general statements, clinical data and laboratory findings will be given for 14 representative cases.

COMPLICATIONS ASSOCIATED WITH THE PRECIPITATING CONDITION

Two complications are commonly associated with the conditions that lead to the development of lower nephron nephrosis, namely *shock* and *vomiting*. Shock of some degree nearly always follows soon upon the initial insult, be it traumatic or nontraumatic. Thus, after crushing injuries, battle wounds, other forms of extensive trauma or burns, a state of shock generally ensues within a few hours. Similarly, in blackwater fever, after incom-

patible transfusions of blood, or after other events precipitating intravascular hemolysis, shock usually develops promptly. Frequently, the signs of shock are unmistakable and comprise significant lowering of the blood pressure, coldness of the extremities, pallor or an ashen appearance. Many cases, however, have no such clear-cut manifestations, but appropriate tests may reveal hemoconcentration as an indication of loss of plasma and of a deficit in the volume of the circulating blood.¹⁴ In other cases shock cannot be demonstrated by clinical criteria, as for example in certain instances of sulfonamide intoxication. Furthermore there is no agreement as to what the syndrome "shock" includes;^{10,66,88} and, since not all cases of lower nephron nephrosis were adequately observed from the very onset of the symptoms, there is no certainty as to whether or not shock always occurred. At present, we must conclude that in the majority of cases shock is a common early complication; whether it is invariably present or essential in the pathogenesis of the renal disturbances is still an open question. It is known that when shock does exist it usually responds to therapeutic measures, so that within less than 24 hours the general state of the patient appears satisfactory.

The other frequent complication is excessive vomiting. It may set in soon after the insult; it may not occur for a day or so, or it may be delayed, and appear as one of the manifestations of terminal uremia. Vomiting was recorded in 9 of the 14 representative cases cited. We shall return to the possible significance of this complication in the discussion.

Urinary manifestations. Diminution in the output of urine occurs so invariably that it is one of the main characteristics of the lower nephron syndrome. Generally, reduction in urinary elimination is noted within the first 24 hours. Since shock itself usually leads to reduction, oliguria may not at first occasion concern. But, usually, despite intake of large volumes of fluid and other measures to restore elimination, oliguria persists and becomes more marked; the daily amount of urine passed is

reduced to less than 500 c.c. Frequently oliguria progresses into complete anuria. Such urine as is passed is generally highly acid in reaction, its specific gravity is low and tends to become fixed at approximately 1.010 (see, for example, case 6). In many cases, the color of the urine may be frankly bloody or smoky for the first day or two. In practically all cases, regardless of its color, the urine gives a positive benzidine reaction, indicating the presence of a heme pigment. This pigment is myohemoglobin (muscle hemoglobin or myoglobin) when the causal condition involves massive destruction of muscle.¹⁷ But, there usually is an admixture of hemoglobin, which may even predominate in some cases of trauma.⁵⁹ The heme pigment which is passed when intravascular hemolysis takes place is hemoglobin. Usually the excretion of either heme component is transitory and no longer demonstrable on the third or fourth day.

Chemical examination further reveals proteinuria of varying degree. This also occurs early, and, unlike myoglobinuria or hemoglobinuria, generally persists throughout the illness.

Microscopically the sediment contains granular and pigmental casts, the latter composed of heme derivatives.¹⁷ In addition, there sometimes are red blood cells, or pigmented spherules of heme which resemble red blood cells.

Chemical composition of the blood. The changes in the chemical composition of the blood reflect the renal shut-down. The level of total nonprotein nitrogen rises rapidly so that by the third day values may exceed 150 mg. for each 100 c.c. of blood. Azotemia was invariably present in all cases of this series in which determinations were made and in which survival was at least 2 days.

As is to be expected azotemia is accompanied by other chemical changes in the blood. Thus for the crush syndrome a progressive increase in potassium and phosphate, and a decrease in the alkali reserve has been reported.^{14,18} At times there is a lowering of the concentration of blood chlorides (as in illustrative cases 5 and 13).

Hypertension. Early but moderate rise in blood pressure is one of the cardinal signs of the lower nephron syndrome. In our series a common sequence was: on the first day, fall to shock levels; on the second day, restoration to normal (which for soldiers of the age group 18 to 38 years ranges around 125/80 mm. Hg.); on the third day, a rise to approximately 150/90; and thereafter the maintenance of this level or a further increase.

Edema. The occurrence of edema is variable. It is usually slight or moderate; sometimes it is generalized; more often it is confined to the lower extremities or to the lungs. Edema of the face is uncommon.

Uremia develops in all cases in which death may be attributed primarily to renal failure and not to the precipitating condition. Typical manifestations usually appear during the last two or three days of life. Vomiting is a frequent feature. The patient becomes irrational or drowsy and lapses into a final coma. Convulsions are uncommon.

Mortality and length of survival. The mortality rate in lower nephron disease is very high. Once the cardinal signs of the syndrome—oliguria, excretion of heme pigment, azotemia and hypertension—have appeared, the mortality is probably in the neighborhood of 90 per cent. The course of the disease is relatively brief. For example, in fatal blood transfusions the survival period usually is from 3 to 10 days.²⁶ In the crush syndrome the end of the first week is said to be the critical period; most patients surviving to the eighth or ninth day, will recover.¹⁴

The length of the survival period after trauma is graphically shown in Fig. 1 for 100 cases of the present series. The polygons give the number of cases (which here is equivalent to percentage); the abscissae show the length of survival. It will be seen that three-fourths of the group (74 per cent) died within eight days; only 8 per cent survived for more than 12 days. Whether death in each case was solely the result of the renal changes, or to what extent the precipitating conditions contributed to the fatal outcome, cannot be ascertained with certainty.

No. of cases

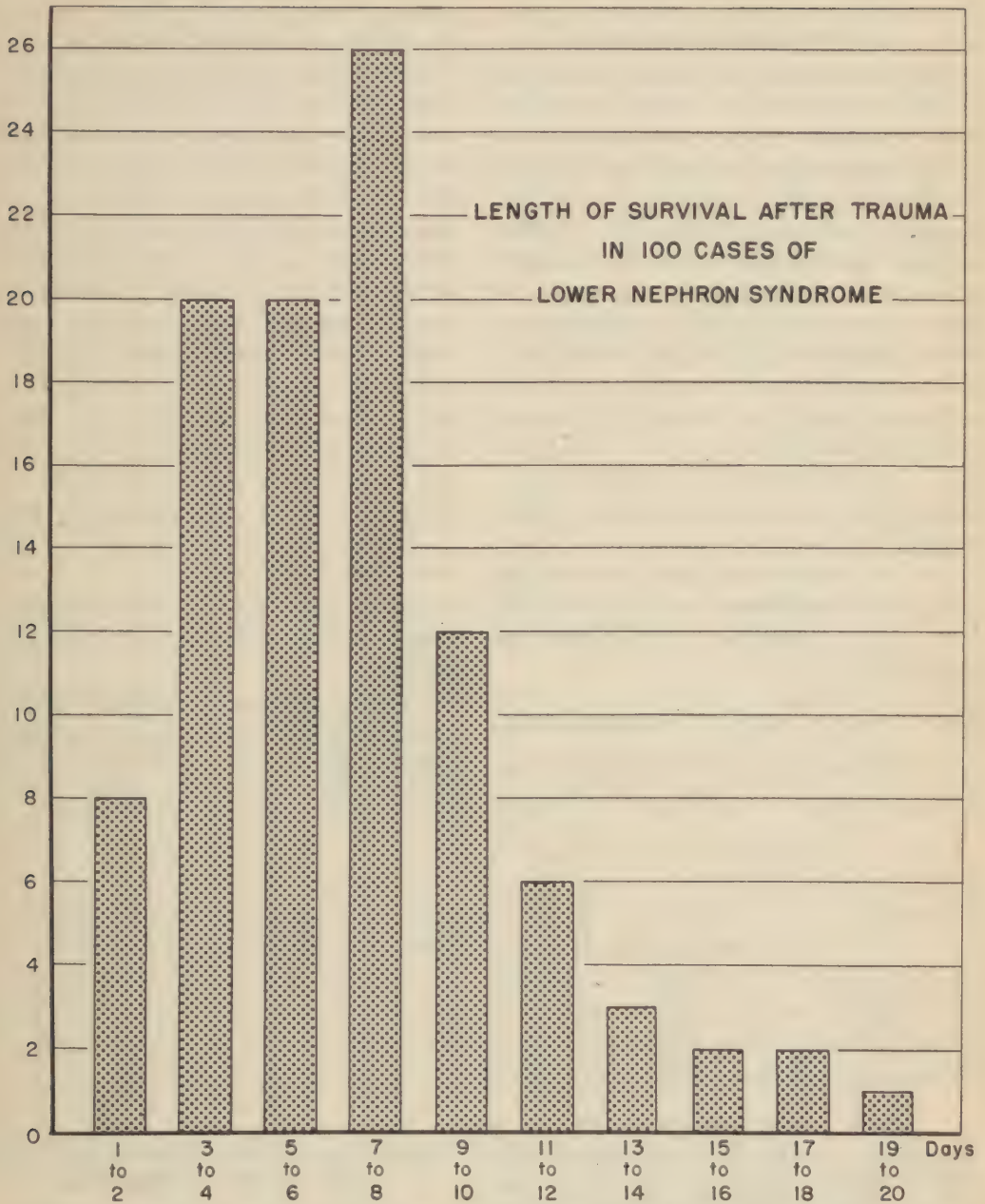


FIG. 1. *Duration of disease.* The polygons represent the number of cases and the abscissae the corresponding duration of disease. It is seen that the great majority succumbed before the 9th day.

ILLUSTRATIVE CASES

Case I (A.I.P. 137402) Crushing Injury

A white male, 25 years old, was buried up to the waist in a cave-in for about 8 hours on November 6, 1944. He voided a large amount shortly after release. On admission he com-

plained of abdominal pains, and later went into shock with a blood pressure of 85/68 mm. Hg. On November 7 he vomited 6 or 7 times, and did not void. On November 9 he voided a few cubic centimeters of acid urine, containing albumin and red blood cells. At this time his

right thigh was hot, tense, and greatly swollen from knee to hip. Blood pressure was now 124/90 mm. Hg. He did not void but 15 c.c. of urine were obtained by catheterization; the specific gravity was 1.012, albumin and red blood cells were present. The blood nonprotein nitrogen was 114 mg. per cent. November 10: Blood pressure was 126/80 mm. Hg.; vomiting continued. November 12: Blood pressure was 132/84; anuria was complete. The patient received several transfusions of plasma and of glucose solution. November 13: Blood pressure was 158/82. He voided 50 c.c. of urine; specific gravity was 1.012; reaction was acid; albumin, red blood cells, granular casts were present. November 15: Blood pressure was 152/86; edema of both legs appeared. The patient died. Duration of illness, 9 days.

Kidneys. Both were greatly swollen and soft. The cortical zones were pale and contrasted sharply with the deep purplish-brown medulla.

Case 2 (A.I.P. 125345). Crushing Injury

A white male, 24 years old, sustained severe crushing injury in an automobile accident on

mm. Hg. It was noted that the patient had eliminated only a small quantity (about 100 c.c.) of urine, which was very dark and bloody. On December 4, the lower extremities were moderately edematous. Transfusions of blood were given. The urinary output appeared to be low, but the exact amount could not be determined. December 5: the general condition seemed satisfactory, but the urinary output continued to be low. Blood pressure was 158/80 mm. Hg. December 6: massive edema of the lower extremities, scrotum, and anterior abdominal wall developed. Only 150 c.c. of urine was passed during 24 hours. December 7: blood pressure was 150/80. December 8: the patient vomited, became irrational, and rapidly went into a deep uremic state, dying at 9 a.m. Duration of illness, 8 days.

Laboratory Data

Urine. 12/1. Color red, reaction acid, albumin 4 plus, microscopically loaded with red cells.

Kidneys. Combined weight 590 gm., greatly enlarged. Capsule thin and tense. Cut surfaces show pale cortex and prominent brownish-red medulla.

CASE 2

Blood

Date	Chlorides (mg/per cent)	NPN (mg/per cent)	Urea N. (mg/per cent)	RBC (millions)
12/3	424			
12/4	480			3.8
12/5	434			
12/6	383	100	32	4.1
12/7	426	175	31	

December 1, 1944. It is probable that his thighs and lower abdomen were pinned-down under a wheel of the car for several hours. When released he was in profound shock; the blood pressure was not obtainable. Shock treatment, including transfusions of plasma, was administered. Later, an exploratory laparotomy was performed, disclosing much hemorrhagic infiltration of the pelvic tissue, but no rupture of viscera. On December 2, the blood pressure had risen to 104/76 and on the 3rd to 143/82

Case 3 (15th Medical General Laboratory 15-A-1407)* Crushing Injury

A white male, 19 years old, was buried beneath rubble in the wreckage of a stone house when a bomb exploded at 1 A.M. on November 22. He was extricated at 4 A.M., but could not be evacuated until after dark, reaching the hospital 13 hours after extrication. He re-

* The abstract of this history was kindly furnished by Lt. Colonel Tracy Mallory.

ceived no intravenous fluid in the interval and no medication other than morphine. Shortly after admission he voided 300 c.c. of dark reddish-brown urine. He seemed in relatively good condition with a blood pressure of 96/76 mm. Hg., pulse of 120, good color and no respiratory difficulty. Physical examination was essentially negative except for the extremities. The muscles of the lower left thigh, the left forearm, right calf and, to a lesser degree, the lower right thigh were tense, hard, and swollen. Pain was elicited by pressure over some of the involved areas, but there was almost total sensory loss over the lower right leg and foot. Pulsations could be felt in the left posterior tibial and dorsalis pedis arteries, but were absent on the right side.

Immediate treatment consisted of shock position, fluids and sodium bicarbonate by mouth, intravenous infusion of 1,000 c.c. of 5 per cent solution glucose, and penicillin. Oliguria developed promptly, the daily outputs running 300 c.c. on November 22, 500 c.c. on November 23, 250 c.c. on November 24, and 100 c.c. on November 25. The urine had a bloody appearance, owing to the presence of a heme pigment which was found chemically to be predominantly myoglobin, though some hemoglobin was also present. On November 24 the blood pressure rose to 164/100 mm. Hg. and remained elevated until just before death. Progressive nitrogen retention occurred, the nonprotein nitrogen level of the blood rising to a maximum of 188 mg. per cent. No whole blood transfusions and no sulfonamides were given. The patient died with severe pulmonary edema on the fourth day.

Case 4 (A.I.P. 90521). Trauma to Muscle; Sulfonamide Reaction (?)

A white male, 22 years old, was admitted on November 8, 1942, with a shrapnel wound of the left leg. Under chloroform anesthesia the wound was debrided and sprinkled with sulfanilamide. The patient was given 1 gm. of sulfanilamide every 4 hours. On November 9 he received 300 c.c. of plasma intravenously. On November 11 the dosage of sulfanilamide was reduced to 1 gm. twice daily. (It is not

known for how long the drug was continued).

On November 18, 20, and 21, secondary hemorrhages occurred in the wound; it was reopened and much old clotted blood and macerated muscle were removed. Between November 20 and 22 five intravenous transfusions, ranging from 125 to 400 c.c., of whole blood or plasma, were administered without reaction at any time. The patient did not void on November 24. The following day 75 c.c. of clear urine was obtained by catheterization. The blood pressure was 100/50 mm. Hg. One liter of glucose solution and 300 c.c. of plasma were given by vein. On November 26 the patient voided 300 c.c. of dark colored urine. Early manifestations of uremia were noted and became more evident during the following day. On November 28 he sank into deep uremia, with Cheyne-Stokes respiration. Death occurred at 10 A.M. Duration of illness, uncertain.

Laboratory Data

Urine. 11/25: straw-colored, acid, specific gravity 1.010, albumin, occasional casts, a few red blood cells.

11/26: dark colored, hazy, acid, specific gravity 1.008, albumin, hematin crystals in sediment.

Blood. 11/26: red blood cells 2.2 millions, white blood count 18,400, hemoglobin 60 per cent.

Kidneys. Combined weight 400 gm. The cut surfaces were moist and showed no noteworthy changes, except that the tips of the papillae were coated with a crystalline deposit which microscopically resembled sulfanilamide.

Case 5 (A.I.P. 63344). Burns

A white male, 22 years old, was severely burned on April 29, 1942, about the face, arms, chest, and right thigh by an explosion of gasoline. On admission he was treated for shock; the burns were sprayed with tannic acid solution followed by silver nitrate; blood plasma and normal saline were administered. Later in the day the patient began to vomit. The morning following the accident he was slightly febrile; his pulse was rapid but of good quality. He received 5 liters of a 5 per cent

solution of glucose in saline intravenously, and later in the day 250 c.c. of blood plasma.

Anuria developed approximately 48 hours after the burn. His blood pressure rose to 160/70 mm. Hg.; the nonprotein nitrogen to 200 mg. per 100 c.c. of blood. He vomited frequently and his condition was considered serious. Vomiting continued throughout the fourth day and on the fifth day the blood pressure rose to 180/90; nonprotein nitrogen was 200 and blood chloride 300 mg. per cent. He voided a small quantity; the specimen contained much albumin and many leukocytes and epithelial cells. On the sixth day he voided 120 c.c. Both lower extremities had become edematous. Nonprotein nitrogen continued at 200 mg. per cent. Red blood cells in the earlier days of his illness averaged 5.5 millions; hemoglobin 90 per cent; white blood cells 22,000; polymorphonuclears 93 per cent. The patient received no whole blood, but a total of approximately two liters of pooled plasma. His condition gradually became worse. He died May 9 on the sixth day after the accident.

Kidneys. Swollen and congested; the cortices were turbid.

Case 6 (A.I.P. 86719). Burns

A 43-year-old white male sustained multiple, third-degree burns on October 15, 1942, from an explosion; approximately one-sixth of his body was involved. His blood pressure on admission to hospital was 120/80 mm. Hg. The burned areas were sprayed with tannic acid solution. The next day one liter of 5 per cent glucose in normal saline and 500 c.c. of pooled plasma were given by vein; the temperature rose to 102 F., and the blood pressure to 140/70. October 18, the patient's general condition was good. The burned areas were well tanned. Two liters of glucose solution were given intravenously. On October 22, the patient vomited repeatedly; his skin was slightly jaundiced; during the following day jaundice deepened. By October 23, the output of urine was approximately 600 c.c. per day, the intake of fluid 4,000 c.c. On October 26 his condition remained unchanged. Urinary output continued at the same rate on the same intake. Blood pressure was 150/50. On October 28 the patient died. Duration of illness, 9 days.

Kidneys. Combined weight was 410 gm.

Laboratory data

Case 6

Blood

Date	RBC (millions)	WBC	Hb. (per cent)	Polys (per cent)	Lymphocytes (per cent)
10/16	5	22,000	14 gm.	92	8
10/22	4.4	13,000		84	16
10/23	4.4	36,000	15 gm.		
10/26	4.6	36,000	15 gm.	92	8

10/24 Total protein 5.57 gm. per cent; albumin 2.56, globulin 3.01.

Date	Icterus Index	NPN (mg/per cent)
10/22	117.6	133
10/23	135	
10/24	124.1	
10/26	93	150

Urine

	Sp. Gr.	Albumin	WBC	RBC
10/18		1 plus		
10/22	1.009	1 plus	20-25 (HPF)	1 (HPF)
10/25	1.007	1 plus	15 (HPF)	
10/26	1.007	1 plus		35-40 (HPF)
10/27	1.008	1 plus	15-20 (HPF)	1 (HPF)

They were swollen and flabby. On section the cortices bulged; the markings were indistinct.

Case 7 (A.I.P. 104707).

Transfusion Reaction

A white male, 37 years old, was injured in an automobile accident on October 28, 1943, sustaining concussion of the brain, compound fractures of the left arm, and multiple lacerations. He was admitted in shock with blood pressure 80/40 mm. Hg.; treatment included transfusion of blood plasma. On October 29 a transfusion of citrated blood was administered. After approximately 250 c.c. had been given, the patient broke out in profuse perspiration, became nauseated and vomited 1,500 c.c. of greenish liquid. Shortly afterwards he had difficulty in breathing, his lips became cyanotic and his respiration of the Cheyne-Stokes type. About 15 minutes after the transfusion he began to have a series of very severe chills, and his axillary temperature rose to 104 F. The condition of the patient improved during the next few days, but his output of urine was very small. The urine was found to be heavily loaded with blood. On November 6 the blood pressure had risen to 190/90 mm. Hg.; the temperature was normal. Oliguria persisted. The patient vomited repeatedly. His breath had a definite urinous odor. On November 9 he fell into a coma and died. Duration of illness 11 days.

Laboratory Data

Urine. 10/28 to 11/4 (several examina-

tions). Specific gravity 1.010 to 1.030; bloody, acid, albumin 4 plus. 11/6: Specific gravity 1.010, acid, albumin 3 plus, many red blood cells.

Blood

Date	NPN (mg. per cent)	Urea N. (mg. per cent)
11/3	111	
11/8	225	76

Kidneys. Combined weight 560 gm. Greatly enlarged and soft. Capsule stripped readily. Cut surface showed a bulging pale cortex, and brownish-red medulla with exaggerated striations.

Case 8 (A.P.P. 92146). Sulfonamide Reaction

A 24-year-old white male was admitted to the hospital on March 10, 1943 with a "cold" of one week's duration. The day prior to admission he had vomited and complained of pain in the abdomen and back. Temperature ranged around 101° F., respirations averaged 22 per minute. The mucous membranes of the upper respiratory passages were moderately congested; the lungs were clear.

Approximately one month before admission the patient had been exposed to meningitis and had received a total of 17 gm. of sulfathiazole. As far as could be learned, no symptoms resulted either from the medication or the exposure. Because of his upper respiratory infection and new exposure to meningitis he was again given sulfathiazole, receiving a total of 13 gm. within 48 hours. His respiratory infec-

Laboratory data

Case 8

Date	RBC (Million)	WBC	Hb. (per cent)	Date	NPN (mg. per cent)
3/11	4.6	10,400	90	3/15	160
3/15	4.5	30,750	80	3/16	150
3/17	3.04		68	3/17	170

Urine

Date	Color	Sp. Gr.	Reaction	Albumin	RBC
3/13	Brownish	1.030	acid	plus	many
3/16		1.018		plus	many
3/18	Brownish	1.019	acid	plus	many

tion cleared, but nausea, vomiting, and pain in back and abdomen recurred. His urinary output rapidly declined; the total amount excreted from March 14 to March 18 was approximately 150 c.c. Blood pressure fluctuated between 125/75 and 175/95 mm. Hg. Pulmonary edema developed rapidly. To relieve respiratory embarrassment phlebotomy was performed on March 14 and 500 c.c. of blood removed; a second phlebotomy was done on March 16 and 600 c.c. removed. On March 17 he had a large gastric hemorrhage. He died March 18 with manifestations of uremia. Duration of illness, 8 days.

Kidneys. Combined weight 410 gm., both markedly swollen. On cut section the parenchyma bulged; the cortices were widened and pale; the cortical markings were slightly dimmed.

Case 9 (A.I.P. 64841). Blackwater Fever

A 30 year old Colombian was admitted on April 3, 1943 with a greatly enlarged spleen and a diagnosis of malaria. On April 2 he had vomited brownish fluid. The temperature was 104 F., the blood pressure 94/20 mm. Hg. The scleras were jaundiced. He did not void between April 3 and April 5, when he passed some blood-stained urine. On April 6 he became irrational; his blood pressure was 92/50 mm. Hg. On an intake of two liters of fluid per day, the urinary output was 105 c.c. On April 7 the patient vomited a great deal. The urine was no longer bloody. The intake of fluid was 1840 c.c., the output of urine 240 c.c. His temperature had been normal since April 4. On April 8, blood pressure was 56/40. The patient died April 10. Duration of illness, 8 days.

Laboratory Data

Blood. On 5 examinations erythrocytes were found to range from 2.2 to 3 million per cu. mm., the hemoglobin from 55 to 65 per cent.

4/10, NPN, 218 mg. per cent.

Urine. 4/5: specific gravity 1.013, acid, large amount of albumin, no bile, benzidine test for blood strongly positive; sediment con-

tained "degenerated erythrocytes."

4/7: specific gravity 1.010; acid, yellow color, trace of albumin, benzidine test negative; no red blood cells in sediment.

4/10: specific gravity 1.010, neutral, straw-colored, albumin 2 plus, sediment contained pus cells and a few red blood corpuscles.

Kidneys. Combined weight 540 gm., enlarged, cortices thickened and cloudy, markings blurred, scattered brownish streaks, and pyramids also streaked with brown. Small pale patches in boundary zone.

*Case 10 (A.I.P. 79906). Arthritis;
Hyperpyrexia*

A colored male, 26 years old, had suffered from recurrent attacks of arthritis involving different large joints of the body. The admission to the hospital on December 23, 1942, was the fifth for arthritis. On December 28 he received an intravenous injection of typhoid vaccine; this was followed by a moderately severe chill, and a rise in temperature to 103° F. On December 29 the injection was repeated. Within an hour a severe chill developed and his temperature rose rapidly to 109° F. Between January 1 and 3 the temperature averaged about 1 degree above normal. The urinary output gradually diminished; after January 3, the volume ranged from 90 to 120 c.c. per day. He was treated by intravenous injections of glucose solution and blood transfusions. Uremic symptoms developed and he died on January 6. Duration of illness, 9 days.

Laboratory Data

Blood

Date	NPN (mg. per cent)
1/3	75
1/4	99
1/5	109

Urine. All specimens after January 5, 1942, contained much albumin, and many red and white blood cells.

Kidneys. Combined weight was 650 gm. On section the parenchyma bulged; the cortical zones were pale and widened; the corticomedullary boundary was indistinct.

Case 11 (A.I.P. 89891). Toxemia of Pregnancy (?); Uterine Hemorrhage

A white female, 22 years old, was admitted in labor on February 19, 1943. Blood pressure was 170/110 mm. Hg. During the third stage, copious hemorrhage occurred, and the patient went into shock; blood pressure fell to a non-readable level. She received two transfusions of plasma, totalling 1,000 c.c., and one injection of 300 c.c. of whole blood. The uterus was packed, but oozing of blood, and shock were not relieved. The uterus was now explored and a piece of placental tissue was found and removed. Since no suitable blood was available a total of 2300 c.c. of a hemoglobin solution was injected intravenously during the next 24 hours. Following these transfusions her blood pressure rose to 150/100. Sodium bicarbonate was administered to keep the urine alkaline. The following day the patient's condition was satisfactory. On the fourth day postpartum the patient voided on an average less than 5 c.c. per hour despite transfusions of citrated blood and glucose solutions. On the sixth day postpartum urinary output increased to approximately 15 c.c. per hour. On the eighth day she became restless, confused, and on the 9th day (February 27) died suddenly.

Kidneys. Combined weight was 600 gm. The cut surfaces exuded a thin bloody fluid. The cortical zones were pale, edematous, and sharply demarcated from the congested medullas.

Case 12 (A.I.P. 18444). Mushroom Poisoning

A white male, 27 years old, on March 13, 1942, developed severe epigastric pain, vomiting, and diarrhea approximately 12 hours after having eaten some "mushrooms." The "mushrooms" were subsequently identified as *Amanita Phalloides*. The urinary output rapidly decreased, and during the 12 days prior to death was alleged to total only 330 c.c. The specimens contained much albumin, numerous erythrocytes, leukocytes and casts. The nonprotein nitrogen of the blood grad-

ually rose to 265 mg. per 100 c.c. Death occurred on March 25. Duration of illness, 12 days.

Kidneys. Combined weight 470 gm.; swollen, edematous, cortical zones widened.

Case 13 (A.I.P. 87529). Alcohol Poisoning

A white male, 37 years old, was admitted on December 6, 1942 after he had been treated for 3 days by a civilian physician for "gastritis," possibly resulting from drinking adulterated alcohol. On admission he was quiet, but soon became restless, excited, confused, and disoriented; the clinical impression was delirium tremens. On physical examination the throat was found to be reddened, there were moist rales over the posterior bases of the lungs. Blood pressure was 136/84; pulse 62. Electrocardiogram indicated marked myocardial damage and right bundle block. The patient continued to be disoriented, and hallucinations developed. On December 8 scleras and skin became jaundiced; on the next day jaundice was more marked. Output of urine steadily diminished to approximately 250 c.c. per day; the specimens had to be obtained by catheter, and were dark colored and bile stained. One liter of 10 per cent glucose solution in saline was given 3 times daily by vein. Because of upper respiratory infection, sulfanilamide was employed; the amount probably was small as the postmortem blood concentration was only 1 mg. per 100 c.c. During the morning of December 10, the blood pressure fell to 82/60. Patient died on this day. Duration of illness, 7 days.

Laboratory Data (12/7 to 12/9)

Urine contained many red cells and granular casts.

Blood

CO₂ combining power 77 volumes per cent.
Chlorides 160 mg. per cent.
Sugar 141 mg. per cent.
NPN 150 mg. per cent.
Urea N 33 mg. per cent.

White blood cells 10,000, polymorphonuclear leukocytes 95 per cent.

Kidneys. Swollen; cortices widened, pale and turbid; medullas grossly normal.

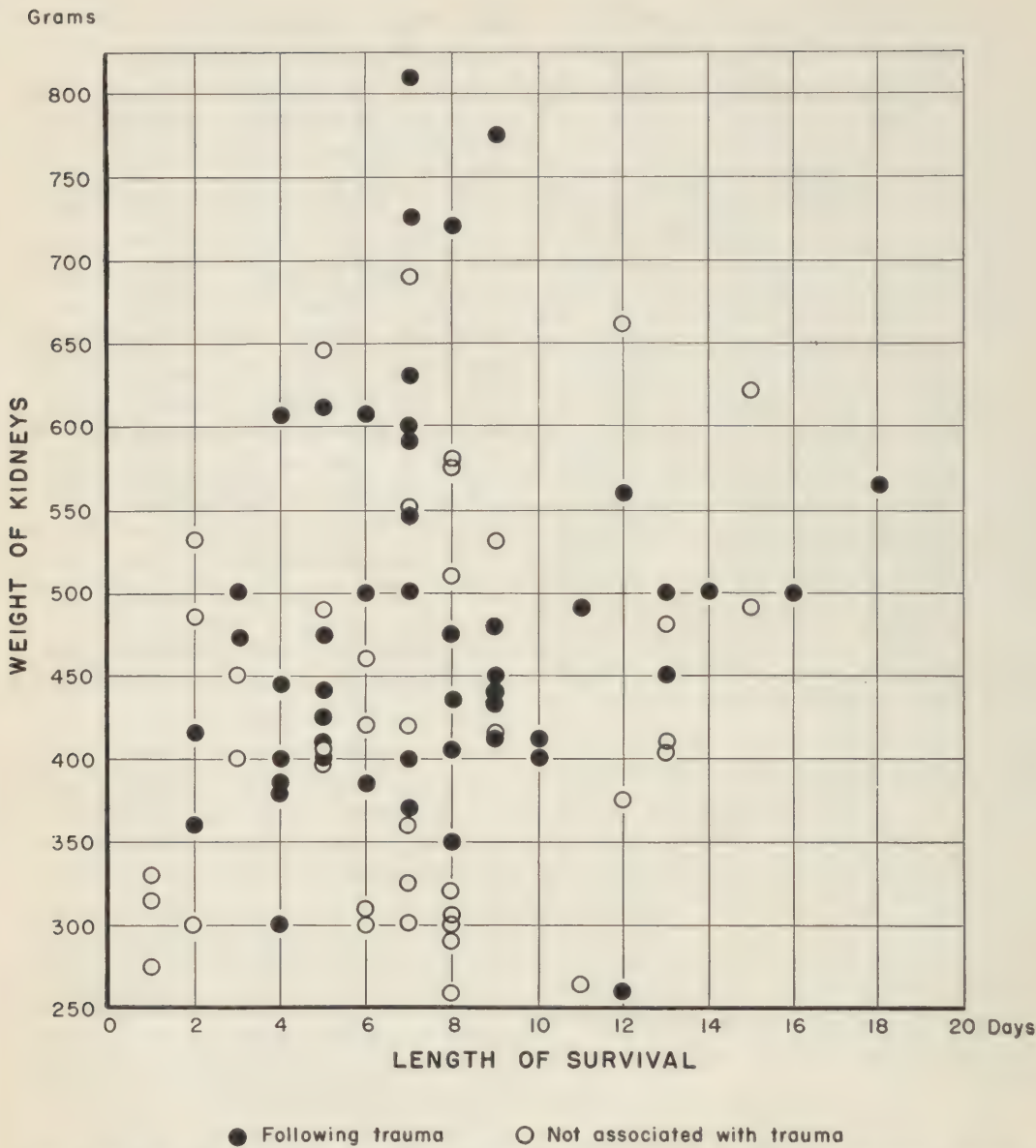


FIG. 2. *Weight of kidneys in lower nephron nephrosis.* The combined weight of the kidneys has been plotted against the length of survival for 89 cases, of which 49 followed trauma and 40 were not associated with trauma. In all but 10 instances the weight of the kidneys exceeds the normal, 300 gm.; the median weight for the group shown is approximately 450 gm.

Case 14 (A.I.P. 90402). Carbon Tetrachloride Poisoning

A white male, 29 years old, on February 1, 1943 accidentally drank an unknown quantity of carbon tetrachloride (the estimated amount was 2 or more ounces). Soon afterwards he became dizzy and had epigastric pains; he took some milk and forced himself

to vomit. The next day he felt well enough to work, but became febrile during that night. Beginning February 2 he was nauseated and vomited after eating.

The output of urine steadily diminished. Thus, on February 7 the intake of fluid was 1980 c.c., the output 810; on February 9, intake 1800, output 560; on February 10

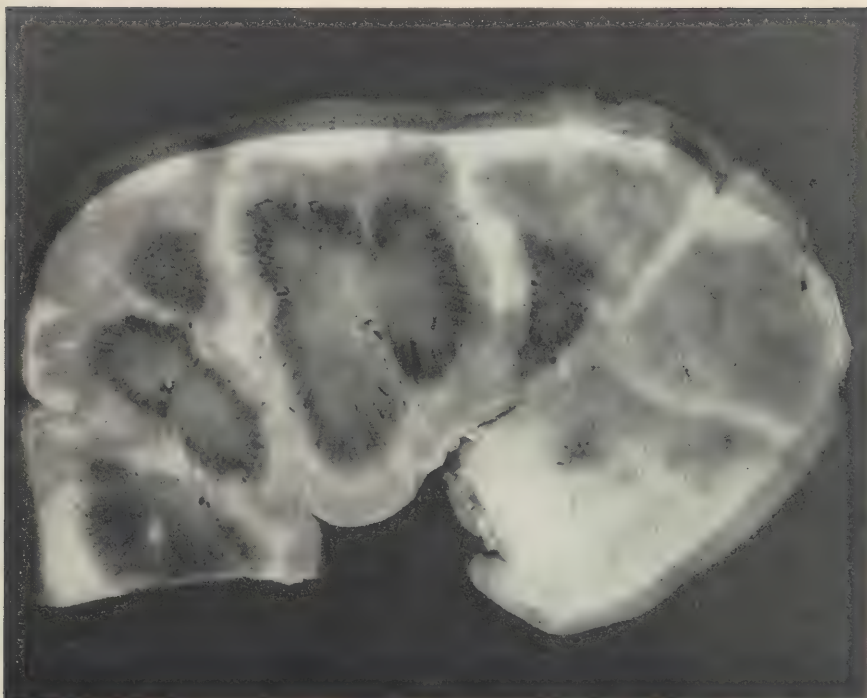


FIG. 3. *Appearance of cut surface of kidney* in a representative case of lower nephron nephrosis. (The combined weight of the kidneys was 500 gm.) The cortex is pale, and here and there shows whitish stripes or patches. The medulla is dark and its striations are accentuated. (Photograph reduced to approximately 7/10 normal size. A.I.P. Acc. 135173)

intake 1350, output 480 c.c. The course continued downhill. On February 5 he became jaundiced. He daily vomited blood stained material. His temperature remained normal until two days before death when it rose to 100° F. On February 11 pulmonary edema developed; the patient became very dyspneic, and died on February 14. Duration of illness, 13 days.

Laboratory Data

Urine

Date	Sp. gr.	Albumin	Casts
2/6	1.007	Trace	Few granular
2/12	1.019	Trace	Granular
2/13	1.020	Trace	Granular

Icterus Index

2/6	35
2/7	50

Blood

Date	NPN (mg. per cent)	Urea N (mg. per cent)
2/12	150	58
2/13	240	45

Kidneys. Combined weight 620 gm.; pale color; cut surfaces bulge; cortical zones turbid; markings indistinct.

PATHOLOGIC ANATOMY

In lower nephron nephrosis organic changes other than those incident to the precipitating condition are largely confined to the kidney. The only other common lesions are edema and scanty petechial hemorrhages on serous or mucous surfaces. We shall here confine ourselves to the changes that may be observed in the kidney.

Gross appearance of the kidney

The gross appearance of the kidneys is not pathognomonic. They are usually swollen and their weight is increased. Thus in 89 cases chosen at random from the present series, the weight in all but 10 exceeded the normal (which, for young adults, averages 300 gm.). In 64 cases the kidneys weighed from 400 to

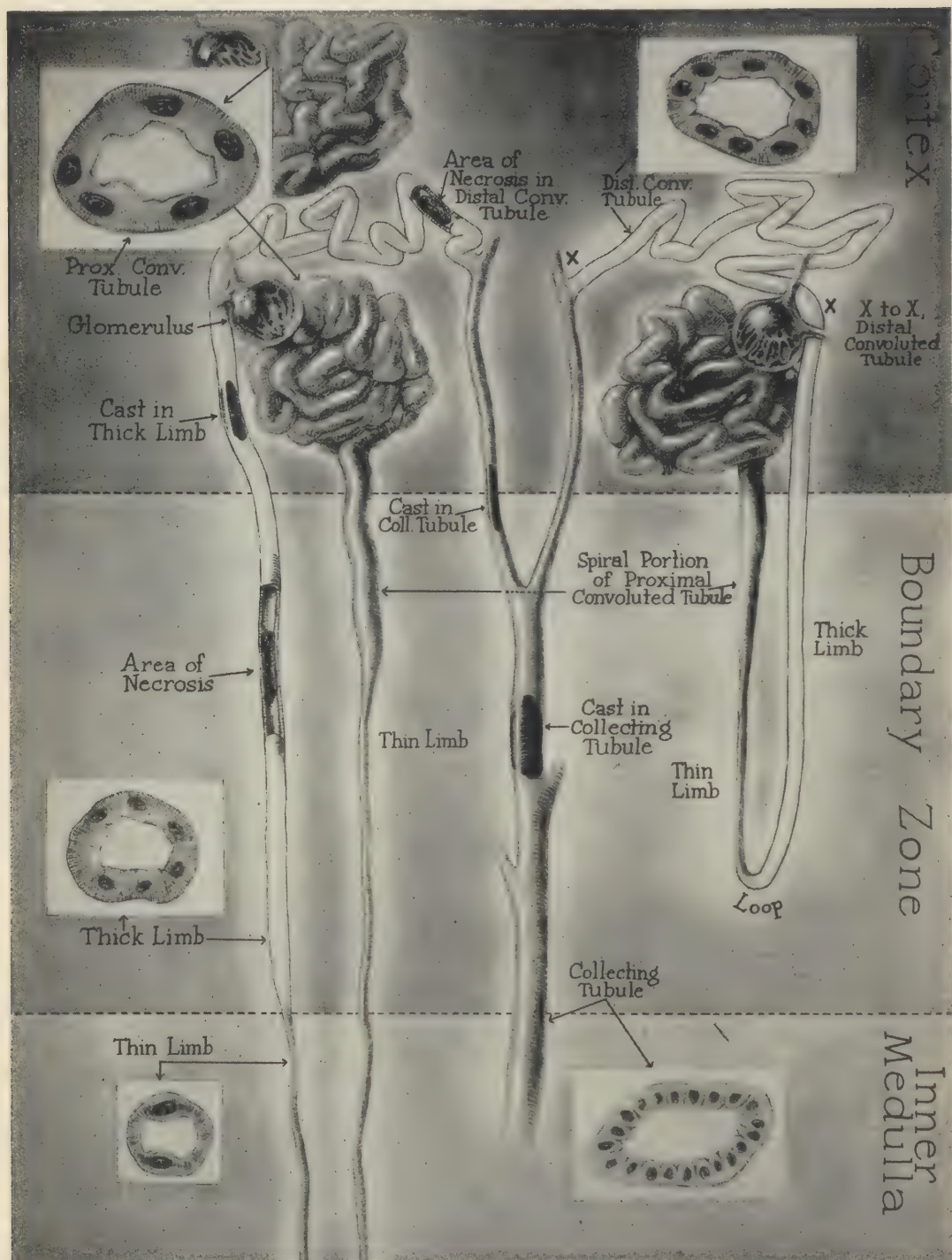


FIG. 4

600 gm., and 13 were more than twice the normal weight. In Fig. 2 the weight of kidneys in individual cases is graphically analysed, first, with respect to duration of disease, and,

second, with reference to the main types of precipitating conditions—traumatic and hemolytic. Considerable scattering of the weights is evident. For example, in 15 cases with a sur-

vival period of 7 days it varied from 300 to over 800 gm. Hence, no definite correlation is found between size of kidney and duration of disease, although there is a tendency for greater swelling when the survival period is prolonged. There is also a suggestion that increase in size after trauma or burns is more marked than after nontraumatic (hemolytic) conditions.

In a typical case, the organ is flaccid; the capsule is easily stripped off; the outer surface is smooth and rather pale. The cut surfaces ooze clear or slightly bloody fluid. The cortex is distinctly widened, bulges perceptibly, is

moist and pale in sharp contrast to the dusky medulla, the striations of which are often accentuated. In the inner zone of the cortex (and sometimes elsewhere) a distinctly whitish stripe is sometimes seen (16); a fairly representative cut surface is shown in Fig. 3.

Microscopic appearance of the kidney

The histopathologic picture of lower nephron disease has four distinctive features:

1. Degeneration or actual necrosis which involves selectively focal portions of the lower segments of the nephrons, i.e. the thick tubules of Henle and the distal convoluted tubules.
2. Edema and cellular reaction which de-

FIG. 4. Diagram of the structure of the normal nephron and of the site of the lesions in lower nephron nephrosis. Each nephron comprises a vascular complex, the renal corpuscle and an attached, unbranching tubule. The latter is differentiated into three principal segments, the proximal (upper), intermediate, and lower. The remaining tubules of the kidney, the collecting tubules, are excretory ducts. Each of the different components has specific functions, characteristic structure, and may sustain selective damage.

Renal corpuscle: The structure and function of the glomerulus and its capsule are too well known to require much comment. Suffice it to recall that the glomerules are filters which daily separate about 150 liters of fluid from the blood. For the filtration of this relatively large amount of fluid it is necessary that both circulation and pressure within the glomerular capillaries be kept at an adequate level.

Proximal segment (upper segment; proximal convoluted tubule). These segments constitute the bulk of the cortical parenchyma. Emerging from the glomerular capsule each forms a compactly coiled mass. Normally the lining cells are large, many have a protoplasmic "hump"; their free surface is covered by a hair-like brush border; their lateral boundaries are indistinct; the cytoplasm is definitely eosinophilic. In its terminal or spiral portion this segment uncoils and, without change in structure, extends into the boundary zone of the medulla. In the proximal segment the glomerular fluid is concentrated by reabsorption of approximately 80 per cent of water; glucose is completely resorbed, and various other modifications take place.^{74, 87}

Intermediate segment. (Thin limb of Henle.) The transition from the proximal to the intermediate segment is abrupt. The diameter narrows from approximately 60 to 20 microns. The epithelium becomes flat and so thin that its nuclei may bulge into the lumen. In general appearance the intermediate segment resembles a capillary. It runs a straight course of greatly variable length. Some segments are short and form a hairpin loop in the boundary zone; others are relatively long and, before looping, extend nearly to the tips of the renal pyramids. The length of the segments depend upon the position of their corresponding renal corpuscles; the nearer the latter are located to the corticomedullary junction, the longer are these tubules. The precise function of the intermediate segment is not known: it may further concentrate the glomerular filtrate; mechanically it has been likened to a pressure trap which slows the flow of fluid within the upper segment, thus prolonging contact with its resorbing surface.

Lower segment. (Thick limb of Henle and distal convoluted tubule.) These two portions are regarded as a histologic and functional unit, i.e. the lower segment. The transition from thin to thick limb may take place in the descending portion, in the loop, or in the ascending portion of these tubules. Usually the change is sudden, the diameter increasing to approximately 40 microns. The thick limbs run a straight course in the boundary zone and ascend into the medullary rays of the cortex, where they turn and approach the vascular pole of the corresponding renal corpuscle. Here, without preceptible change, they become the distal convoluted tubules. The latter run a zig-zag course between coiled masses. Because of their angulations, several cut sections of the same lower segment usually lie as a group within a field of the microscope. Compared to the proximal segment, the cells of the lower segment are smaller, more numerous, and lower; they lack a brush border; their cytoplasm is but faintly eosinophilic, and, in sections stained with hematoxylin-eosin, the cytoplasm may even have a slightly bluish tint. In the lower segment, the intertubular fluid becomes acidified and undergoes its final modifications before being emptied as urine into the collecting tubules.⁸⁷

It is in the lower segment, and in the adjacent stroma and its thin-walled veins, that the principal lesions of lower nephron nephrosis are located. As indicated in the diagram the segment is usually not involved throughout its length, but in a patchy, focal manner.

Collecting tubule. The collecting tubules are not part of the nephrons but excretory ducts that convey the now completely modified glomerular filtrate, i.e. the urine, to the renal pelvis. They begin in the cortex, run a straight course through the rays, the boundary zone and the medulla, to the apex of the papillae, their caliber gradually increasing. Their epithelium is clear, the cell boundaries are well defined, the nuclei sharply outlined, the cytoplasm basophilic. The collecting tubules are rarely damaged to a significant degree, but their lumens may be packed with heme casts.

velop in the stroma around the more severely damaged or disintegrated portions of the tubules; these changes are commonly associated with thrombosis of the adjacent veins.

3. Casts of a heme compound which lie within the lumens of variable numbers of the lower segments and of the collecting tubules.

4. Relatively slight or no structural changes in the upper parts of the nephrons—renal corpuscles, proximal and intermediate segments.

It is clear that the damage in this disease is essentially confined to a particular component of the nephron. The identification of the several components is not difficult; their appearance and location are shown diagrammatically in Fig. 4. Here also is indicated the site of the tubular lesions. We may now consider the histopathologic picture in greater detail.

The renal corpuscles. The glomeruli are normal in size and cellularity; their coils are patent, but commonly their blood content is poor, suggesting inadequate circulation.^{28,47,56,90} The capsular spaces usually are of normal width;²⁸ dilatation, such as occurs when tubules are completely obstructed, is rare. Nearly always, the spaces contain an abundant eosin-staining, granular, foamy, or globular protein precipitate,^{16,30,90} indicating an increase in glomerular permeability. Cuboidal swelling of the normally flat epithelium that lines the capsule is sometimes observed, especially near the mouth of the tubule. The cellular swelling may be related to the leakage of proteins through the tufts, since renal epithelium is to some extent capable of absorbing proteins.

An interesting change has lately been described in the juxtaglomerular apparatus;⁴⁷ in cases of crush injury marked hypertrophy and increased granularity of the cells were noted. Systematic examination of our own material has not as yet been carried far enough to determine whether similar changes occurred.

Proximal segment. The appearance of the lining cells of the proximal segment is often quite normal; even their delicate brush border is well preserved. At times, however, the cells

are slightly swollen and somewhat more granular, that is to say they exhibit "cloudy swelling." Occasionally fatty deposits are disclosed by appropriate staining; frank degeneration or actual necrosis is very rare. The lumens of the tubules sometimes seem slightly dilated, and commonly contain a protein precipitate similar to that in the capsular spaces, whence it probably has been washed down (Fig. 5, 6, and 11). Heme casts are very rarely observed in this segment.

The comparative absence of significant damage in the proximal tubule is of interest. Most renal poisons—mercury, uranium, oxalates, tartrates and cantharidin—damage this segment almost or quite exclusively.^{31,32,33}

Intermediate segment. Definite changes can seldom be found in the intermediate segment; there is neither obvious cellular injury nor precipitation of heme compounds.

Lower segment. It is widely agreed that the lower segment is damaged selectively in the various conditions mentioned in the introduction. For example, such selective damage has been reported in cases of crush injury,^{16,30} in burns,^{46,53} in blood transfusion fatalities,^{8,26} in uteroplacental damage,⁹⁰ in sulfonamide intoxication,^{42,52} and after excessive vomiting.⁵⁵

In summarizing the microscopic appearance, it is convenient to describe, first, the changes in tubular structure, and then the casts within the tubules and the reactions in the neighboring stroma and the vessels.

1. *Tubular alterations.* The damage primarily involves the tubular cells. It varies widely in degree from slight degeneration to frank necrosis and complete disintegration. In general, when the survival period is less than three days the regressive changes are relatively inconspicuous and are indicated chiefly by increased granularity and by minute droplets of fat. More definite degeneration or frank necrosis may be seen by the third or fourth day. In distribution, the lesions are characteristically focal, affecting small areas rather than whole segments, many of which appear to escape damage entirely. At times the most pronounced lesions are in the boundary zone, or

FIG.
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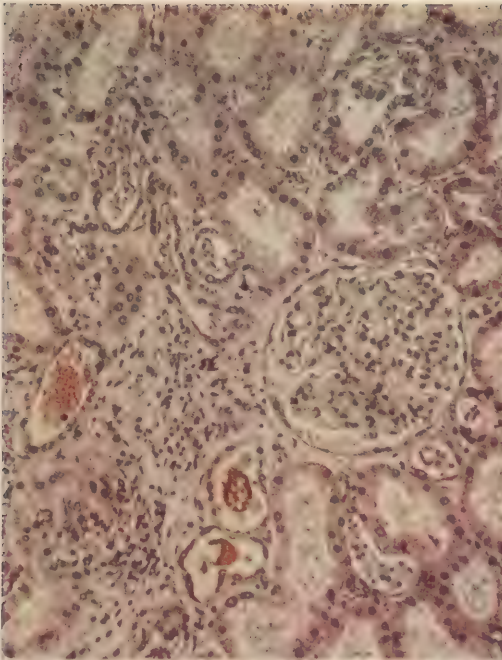


FIG.
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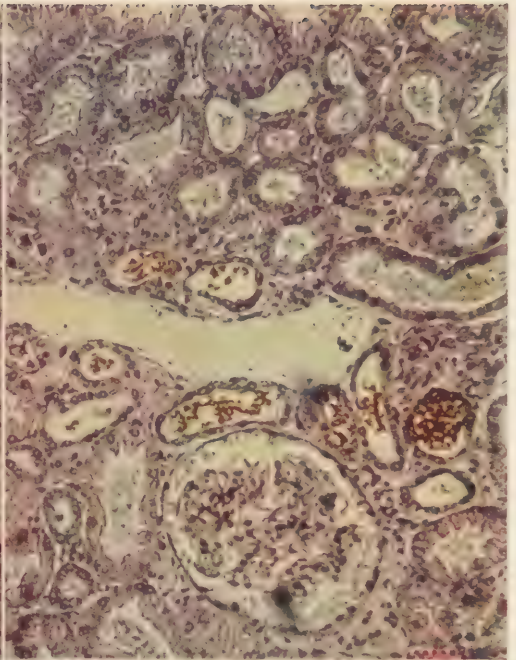


FIG.
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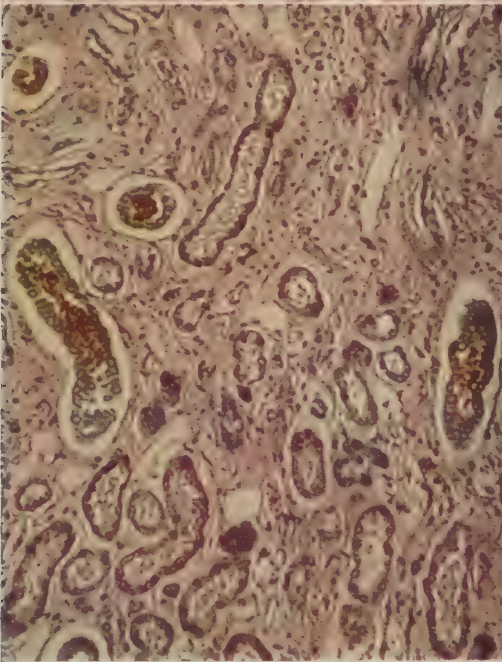


FIG.
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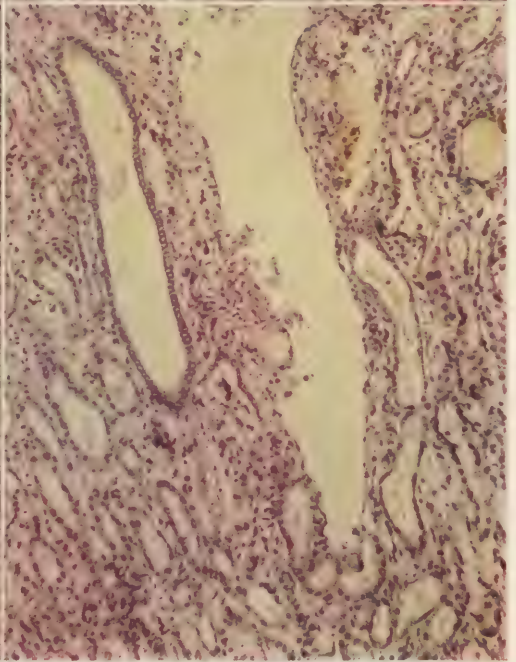


FIGURE 5. Pigment casts in distal tubules. Area of tubular destruction and interstitial inflammatory reaction. The glomerulus and the proximal tubules show little alteration. Case of transfusion (AIP Acc. 79906).

FIGURE 6. Pigment casts in lower tubular segments adjacent to a thin-walled vein. Protein precipitate in glomerular space and in proximal tubules, which otherwise are normal. Case of burns (AIP Acc. 83444).

FIGURE 7. Interstitial edema. Several distal segments have disappeared completely; other segments are degenerating or contain pigment casts. Case of mushroom poisoning (AIP Acc. 81444).

FIGURE 8. Parietal thrombus in thin-walled vein, probably resulting from rupture of necrotic tubule into vein. Case of crush injury (AIP Acc. 81070 A).

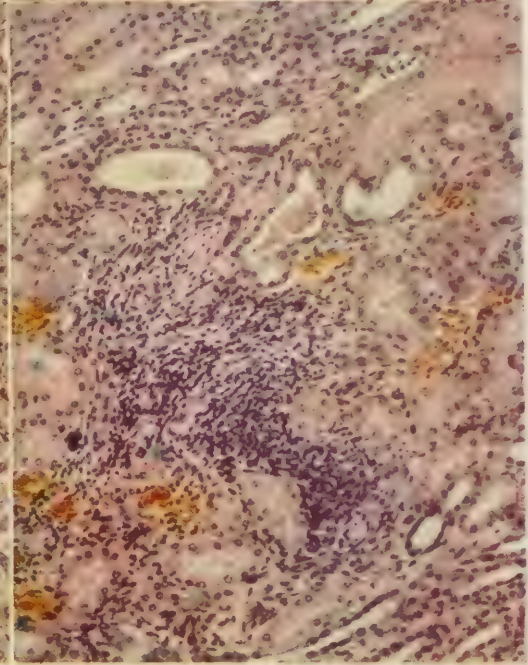
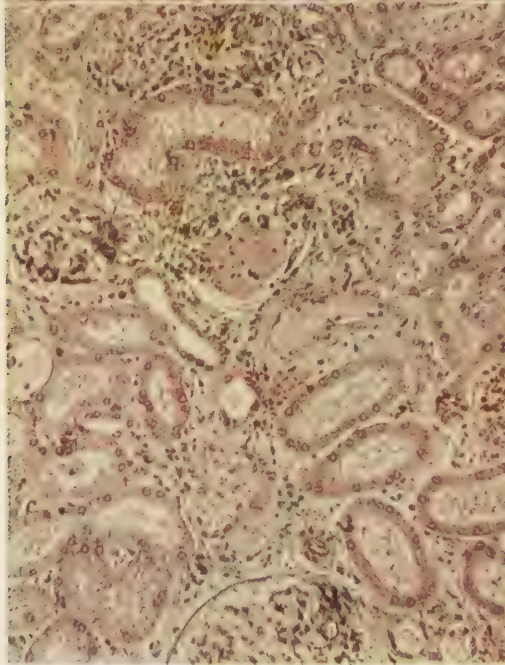
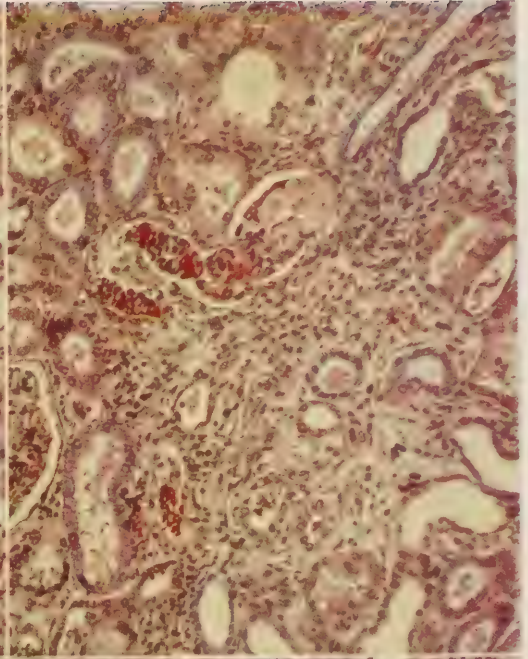
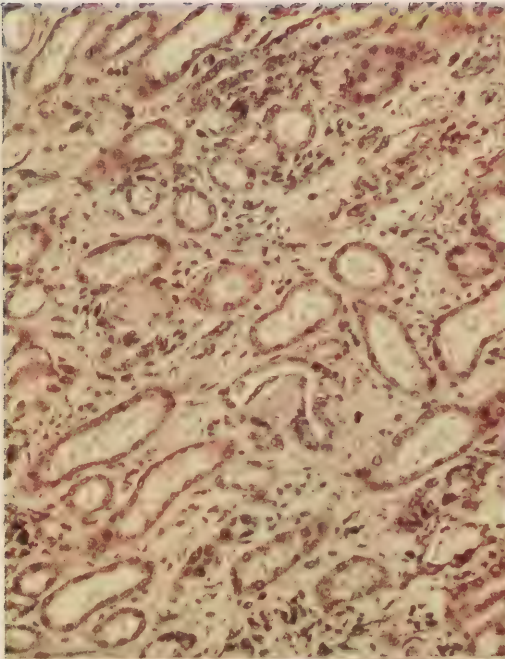


FIG.
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FIG.
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FIG.
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FIG.
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FIGURE 9. Interstitial edema. Disintegration and early regeneration of the lining of several distal segments. Dense hyaline cast in a dilated tubule. Case of crush injury (AIP Acc. 81070 A).

FIGURE 10. Area of tubular disintegration and inflammatory reaction. Pigment casts, and one large "mixed" cast. Case of burns (AIP Acc. 83444).

FIGURE 11. Area of tubular disintegration and interstitial cell reaction. Hyaline cast in a disintegrating segment. Normal proximal tubules, with protein precipitates in lumens. Case of burns (AIP Acc. 83444).

FIGURE 12. Area of tubular disintegration and inflammatory reaction. Pigment casts. Case of sulfathiazole intoxication (AIP Acc. 92146).

at points where the lower segments lie in close proximity to veins.^{16,30} Obvious dilatation of the lumens is relatively uncommon, but local outward bulging (herniation) or actual rupture of necrotic portions is frequent. It is interesting to note that diverticula are common in the lower segment; excellent photographs of them are given in a recent paper by Oliver.⁶⁷ From about the fifth day onward, the remnants of necrotic portions of tubules may undergo complete disintegration and disappear (Fig. 5, 7, 10, 11, 12).

Where the destructive process is not so intense, and when the survival period has exceeded 3 or 4 days, regeneration is evident. Through proliferation of epithelium that has escaped irreversible injury, new cells creep beneath the dead lining. The latter becomes detached and is cast off into the lumen where it further disintegrates. The new cells differ from the pre-existing epithelium; at first they are thin and flat, resembling endothelium; later they become cuboidal in shape. In the early stages their cytoplasm is distinctly basophilic, and the nuclei are richly chromatic. The healing process proceeds rapidly; within less than 10 days most damaged areas are completely relined.

2. *Casts*. Aside from cellular debris two kinds of casts are common within the lumens.

The most conspicuous casts are pigmented masses of a *heme* compound; they are the most prominent, though probably not the most significant feature in the histopathologic picture (Fig. 5-7, and 10-16). After destruction of muscle, the pigmented masses are composed predominantly of myohemoglobin or derivatives thereof;¹⁷ in hemolytic conditions they are formed by hemoglobin and its degradation products. Both types of heme casts are microscopically alike, and their staining properties are similar. In unstained preparations they have a reddish hue; in sections stained with hematoxylin and eosin they usually are brownish or copper colored. Some are smooth and solid in texture (Fig. 13), others granular (Fig. 13, 16); frequently they look like strands of coarsely beaded wire or frayed ribbons (Fig. 14); at times they have the form of

spherules which may be mistaken for erythrocytes (Fig. 15). The casts do not give a reaction for free iron, but in their earlier stages they have the tinctorial reactions of hemoglobin.

These heme masses are relatively scanty in the beginning straight part of the lower nephron; they become more numerous in the convoluted portion. They are often particularly prominent in tubules immediately adjacent to thin-walled veins (Fig. 6).

The number of segments containing casts varies greatly in different cases; rarely they are entirely absent, in some cases they must be searched for, in others they are conspicuous in every microscopic field. They are infrequently found when the survival period is less than 2 days. However, unlike the pigment excretion in the urine, which lasts but a day or so, the casts in the tubules usually persist.

The second kind of cast is nonpigmented, hyalin in texture, stains faintly with eosin, and resembles a dense coagulum of protein (Fig. 9, 11). It is much less common than the heme cast, and tends to occur only in portions of tubules that have been severely injured. It lies more often in the straight than in the convoluted portions of the lower segment. The lumens of affected tubules are completely obstructed, and upstream from the point of blockage may be definitely dilated. Through rupture or disintegration of portions of the tubule these casts are extruded into the stroma.

3. *Stroma*. The interstitial tissue around foci of tubular disintegration is edematous and exhibits an inflammatory reaction (Fig. 5, 7, 9-12). At first, the participating cells are predominantly lymphocytes and histiocytes; granulocytes are usually scanty and giant cells occasional. At later stages, fibroblasts make their appearance, and when survival exceeds a week, the destroyed parenchyma is replaced by recent scars.

The areas of edema and cellular reaction in the stroma are as a rule small and scattered, although they may be numerous. They conform with sites of tubular necrosis; the foci may be especially prominent in the boundary zone, in the cortex near glomeruli, around

venous channels, and around extruded casts.

4. *Involvement of veins.* Some of the large venous channels of the kidney, especially those in the boundary zone, have a unique structure: they are so exceedingly thin walled that normally the adjacent renal tubules bulge into their lumens. When tubules become necrotic, they may rupture into a vein, spilling their contents and inducing thrombosis.^{8,16,30,52,55}

The thrombi usually are parietal (Fig. 8), rarely occlusive. Remnants of epithelium are commonly found embedded in the clot. The walls of the veins are often infiltrated with inflammatory cells. Some tubulovenous lesions occur in the majority of cases having a survival period of more than five days.

Collecting tubule. Conspicuous degenerative changes rarely involve the collecting tubules. The majority appear normal, only an occasional tubule is found partly stripped of its epithelium or relined by regenerated cells, which may become heaped up.¹⁶ Casts of heme compounds, however, are usually more conspicuous in these tubules than in the lower nephron (Fig. 14, 16); they are larger, and fill longer stretches. At times they become coated by epithelial cells and attract leukocytes; heme casts in the lower nephron seldom exhibit either of these phenomena. It seems probable, therefore, that the casts in the collecting tubules represent an older and more advanced stage of degeneration of the heme compounds. The number of collecting tubules involved and the completeness of obstruction vary greatly.

PATHOGENESIS AND FUNCTIONAL DISTURBANCES

From the many problems concerning pathogenesis of lesions, and mechanism of functional disturbances we have singled out several for brief discussion: What part is played by heme compounds, by products of tissue breakdown, by disturbances in the physicochemical composition of the blood, by shock and renal vasoconstriction in the production of the specific renal changes? What is the mechanism of oliguria; does it involve extrarenal factors?

None of these questions can as yet be an-

swered, rather a discussion of them may point the way to further investigation. Moreover, the several questions are difficult to separate, for the factors concerned are interrelated. It will be seen that no single hypothesis can satisfactorily account for the renal disturbances;^{34,40} perhaps several factors act conjointly, their combination depending upon the precipitating condition.

Role of heme compounds

Characteristic of the renal lesions is the almost constant presence of heme casts. As has already been stated, two kinds of hemoglobin compounds are involved, myohemoglobin, and hemoglobin. These two compounds differ in various respects,⁶² but it is fair to assume that the role they play in regard to the renal disturbances is similar. We shall consider, first, how these compounds are excreted by the kidneys; second, why they are precipitated in the lower segments, and, third, whether they or any of their degradation products are toxic.

Excretion of heme compounds of kidneys, (a) *hemoglobin.* When destruction of red cells is great, as in extensive intravascular hemolysis, not all the liberated hemoglobin can promptly be metabolized into bile pigments, and much of it passes through the glomerular filters.^{38,91} The manner in which this passage takes place is a matter of dispute. The glomerular capillaries may be regarded as thin membranes, containing liquid-filled pores of various size through which a filtrate can be expressed by a "blind physical force," i.e., by hydrostatic pressure.⁷⁴ It is generally accepted that the pores of the membranes are smaller than the diameter of the molecule of serum albumin, the molecular weight of which is approximately 70,000, and which normally does not escape through the glomerulus. Since the hemoglobin molecule has very nearly the same weight, several possible explanations have been advanced for its passage: (1) that a small proportion, perhaps 3 per cent, of the capillary pores are sufficiently large to permit penetration of hemoglobin; (2) that hemoglobin may dissociate into molecules of smaller dimensions which can pass through most of the

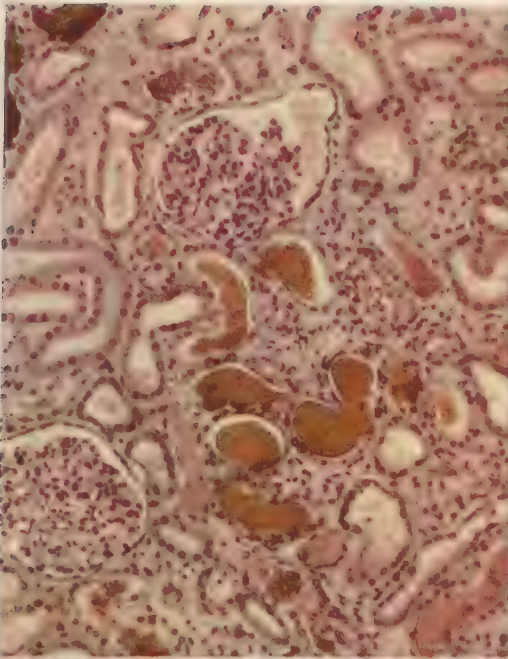


FIG.
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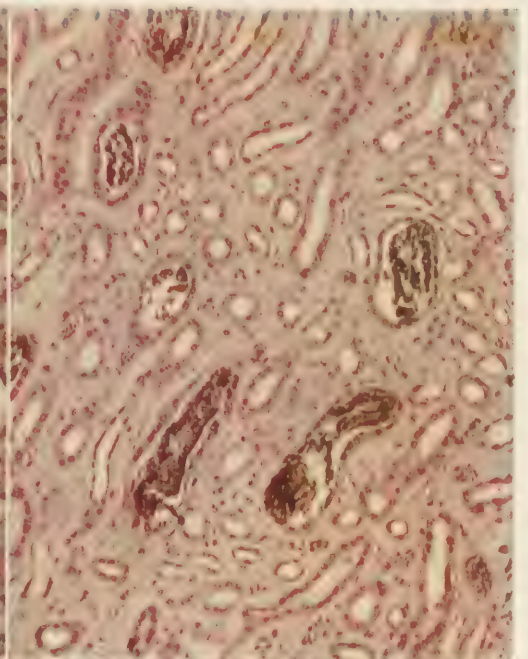


FIG.
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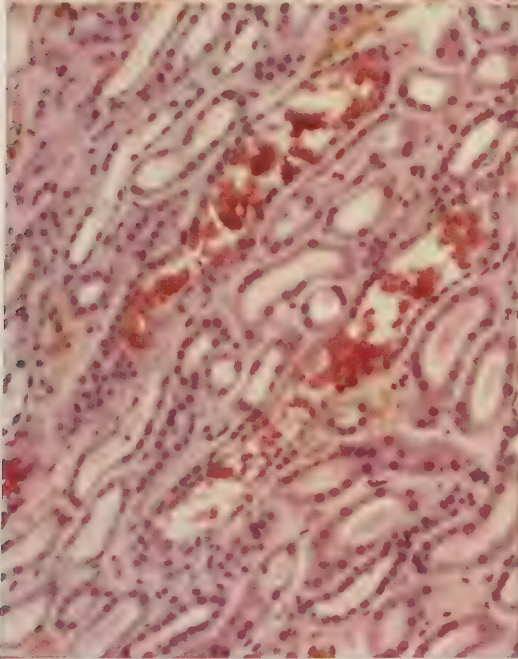


FIG.
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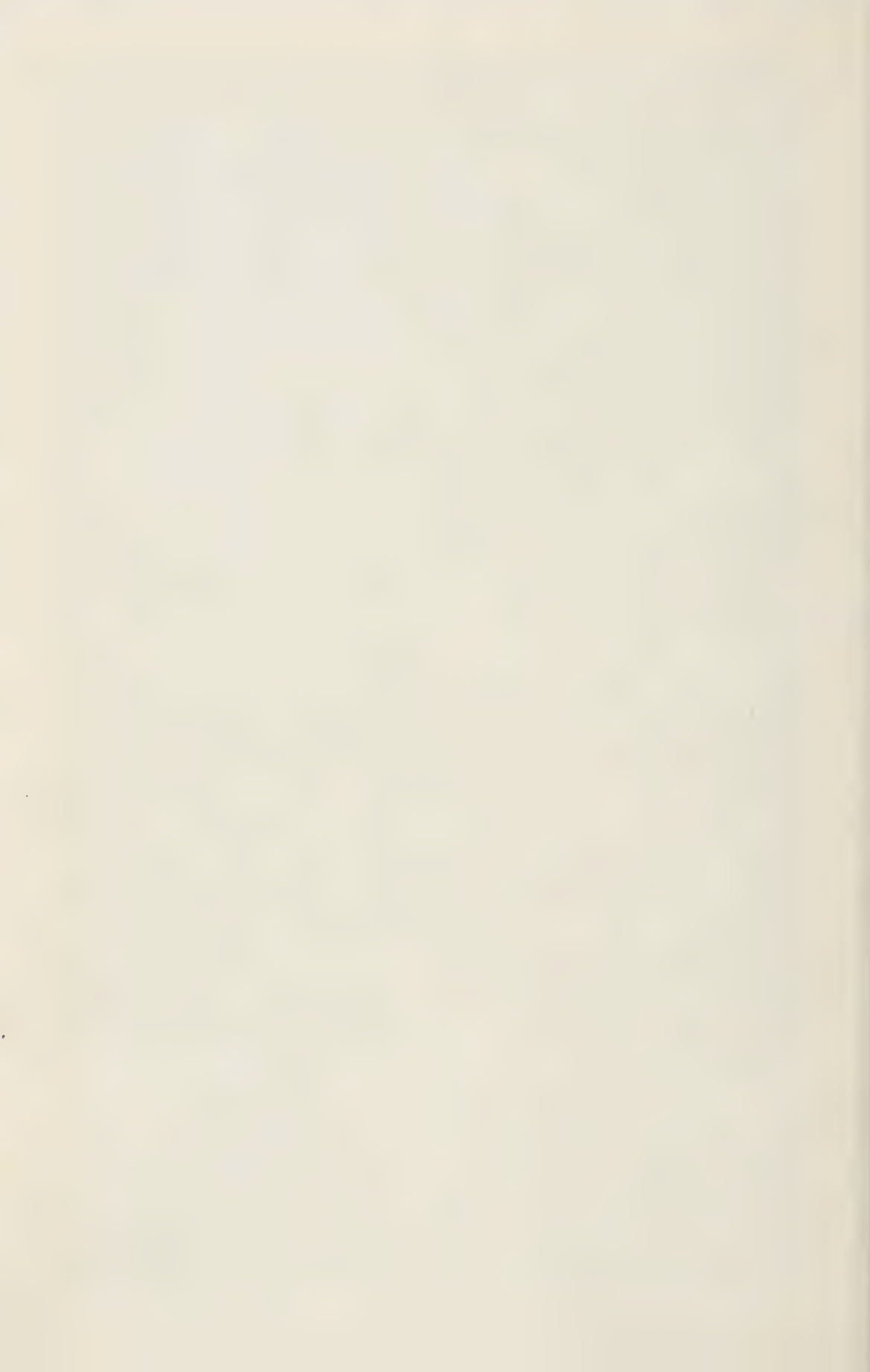
FIG.
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FIGURE 13. Smooth (recent) and granular (older) hemoglobin casts in distal tubules; the older casts lie in segments adjacent to the glomeruli. Case of eclampsia and hemoglobin transfusion (AIP Acc. 89891).

FIGURE 14. Copperwire-like heme casts in collecting tubules. Case of transfusion (AIP Acc. 79906).

FIGURE 15. Heme casts composed of spherules which resemble erythrocytes. Case of heat stroke (AIP Acc. 120161).

FIGURE 16. Dense granular heme casts in collecting tubules. Case of crush injury (AIP Acc. 81070 B).



pores of the normal glomerular capillaries; and (3) that glomerular permeability is increased, i.e., that all of the pores are widened. For detailed discussions of these opposing views the papers of Yuile,⁹¹ Botts and Richards,¹¹ and Foy, Altmann, Barnes and Kondi⁴¹ should be consulted.

Here we shall consider only the hypothesis that glomerular permeability is altered. It is a known fact that permeability of living cells may be made to increase considerably without inducing detectable changes in structure; within a relatively wide range such an increase is reversible. Now, it has been demonstrated that hemoglobin, when its concentration in the plasma exceeds a certain level, exerts a specific, transient vasoconstrictor action on renal arterioles.⁶¹ It has also been found that renal vasoconstriction, produced experimentally by several means in man and in animals, leads to transient albuminuria through increase in permeability of the glomerular capillaries,⁸⁰ no structural alterations are evident and the effect on permeability is reversible. It has further been shown in human experiments, that albuminuria appears in all cases in which sufficient hemoglobin is injected intravenously to induce hemoglobinuria.⁴⁴ These experiments support the hypothesis that hemoglobin is excreted by the kidney, in large quantities at least, only when the permeability of the glomerular filters is increased. It is very probable that this change is effected primarily by arteriolar vasoconstriction, which subsequently through oxygen lack leads to alterations in capillary permeability. Renal vasoconstriction, as we shall see, is a factor of prime importance in the production of the structural and functional disturbances in the kidney. Hence, the mechanism of hemoglobin escape is not only of interest in itself, but also in that it focuses attention on vascular constriction in the kidney and on changes in glomerular permeability.

(b) *Myohemoglobin.* The molecular weight of myohemoglobin is 17,500, which is sufficiently small to permit its ready passage through unaltered glomerular capillaries. But it is probable that the conditions which lead to liberation of myoglobin from injured muscle

cells also bring about renal vasoconstriction and an increase in permeability of the glomerular filters. That permeability is definitely increased is demonstrated clinically by the almost invariable occurrence of proteinuria, and histopathologically by the protein precipitates seen in sections.

Precipitation of heme compound in the lower segments of the nephron

It is known of hemoglobin, and it is probably true of myoglobin, that when it has passed through the glomerular filter, a relatively small portion is reabsorbed by the cells of the proximal segment, through a process akin to phagocytosis.⁹¹ The larger portion of the pigment remains in solution until the lower segment is reached. Here some of the heme compound may be removed from solution by precipitation caused by factors only partially known.

According to one hypothesis, that of Baker and Dodds,⁴ hemoglobin is thrown out of solution, probably as hematin, when the intratubular fluid becomes sufficiently acid (below pH 6.0), and when simultaneously through absorption of water the concentration of sodium chloride is increased to about 1 per cent. These requirements are met in the lower nephron⁸⁷ and in the collecting tubules. In analogy with these experiments on hemoglobin, it has been shown by Bywaters and Stead¹⁹ that intravenous injections of myohemoglobin may lead to renal failure with pigment retention when the acidity of the urine reaches levels of pH 4.5 to 6.1.

The hypothesis that acidity of the urine is of prime importance in the genesis of renal damage has led to widespread therapeutic use of alkalization in cases of severe muscle trauma or intravenous hemolysis. But there is some evidence that hemoglobin and its products, as well as other solutes, are more readily secreted in an acid than in an alkaline urine.^{28,40} It has also been pointed out that blood transfusion fatalities may occur when the reaction of the urine is persistently alkaline;^{28,40,91} and, similarly, that in blackwater fever, anuria is no more common in patients

with acid than with alkaline urine.⁴⁰ It is obvious that further investigation of this important question is demanded.

Another hypothesis relates the precipitation of heme compound to cellular injury.^{40,90} Some support of this view has been obtained in recent experiments. It was shown by Yuile, Gold and Hind that heme pigment is precipitated in tubules previously damaged by ischemia or by chemical poison.⁹² Cellular injury in the lower nephron, like precipitation of heme compounds, has been attributed to the acid reaction of the intratubular fluid in the segment.^{30,31,54}

It has also been suggested that the inadequate flushing of the tubules due to lowered filtration pressure may be a factor leading to accumulation and retention of pigment masses within the tubules.⁴⁰

In connection with these unsolved questions, certain points made by Oliver in his recent Harvey Lecture⁶⁷ are pertinent. When nephrons are dissected out in their entirety, it may be seen more clearly than in sections that coagula and casts are not found in all parts of the tubular system, but that they occur particularly in the lower half, i.e., in the distal and the collecting tubules. Evidently conditions there are favorable for coagulation of protein-containing fluids. Referring to older work on the so-called x body, a substance normally present in urine and a factor in coagulation, he reports experiments which lead him to the conclusion that proteins attain the isoelectric point necessary for coagulation only when the glomerular filtrate reaches the distal tubules; here, since the concentration of the x body is high, cast formation takes place.

Are heme compounds toxic? It is generally accepted that solutions of pure hemoglobin or myohemoglobin as such are not nephrotoxic.^{1,4,8,28,40} Discrepancies in results of experiments are probably explainable on the basis of variation in the preparation of solutions and on species differences. As Foy⁴⁰ points out, hemoglobin metabolism in man is not comparable with that in dogs, cats, or rabbits and the results of hemoglobin injection into lower animals should not be unqualifiedly referred to man.

When nephrotoxic effects follow injections of either hemoglobin or myoglobin, they are generally attributed to abnormal breakdown products or derivatives. Some investigators hold that such toxic derivatives are most apt to form when the reaction of the urine is acid.^{4,19,22} The exact nature of these substances is doubtful, but it seems to be experimentally established that hematin (sodium ferrihemate) exerts definite injurious effects, and produces lesions which resemble those of human lower nephron disease.^{1,21,22} This substance is released from heme-globin linkage during the degradation of either hemoglobin or myohemoglobin. It causes intense renal vasoconstriction and tubular damage.²² The nephrotoxic effect of methemoglobin⁸ in dogs which have been rendered acidotic is perhaps also due to release of hematin.

Whether heme derivatives act directly on tubular cells or whether the intratubular heme casts are injurious is uncertain. Some observers believe that heme casts are not necessary for the development of the renal lesions,^{3,90} and that, as already stated, the casts are the consequence not the cause of the tubular damage.^{40,92} But heme precipitates, no matter how induced, will probably aggravate cellular injury caused by other factors.⁹¹

In sum, information concerning the part played by heme compounds in the genesis of renal disturbance is still incomplete. But it seems to be established that these compounds are not the sole agents of tubular damage.

Nephrotoxic substances arising from injured tissue

Many observers maintain that in cases of crush injury and other forms of muscle trauma, a toxic substance, or substances, may be liberated from the damaged tissue into the blood stream, effecting renal damage in the course of its excretion.^{21,23,30,45,72,90} It is a known fact that some products of tissue breakdown have toxic properties, but the particular agent responsible for the renal damage is as yet unknown. One of the agents suggested on the basis of experiments is adenosine triphosphate.^{6,7,81} It has been shown that an extract can be obtained from muscle which on

injection will produce nephrotoxic signs and symptoms. The effect is accentuated by simultaneous injection of myoglobin. The greater part of the activity of the extract has been attributed to adenosine compounds, and an increased concentration of these compounds has been demonstrated in the blood returning from ischemic muscle.⁸¹ By other experiments it has been demonstrated that a substance toxic to the kidney can be extracted from ischemic muscle but not from normal muscle.^{34,35} The toxic factor may be some early breakdown product of large organic molecules (perhaps proteins) formed only under prolonged anaerobic conditions. The interesting suggestion has been made that if this substance is liberated slowly into the bloodstream, the liver is able to detoxify it, so that the kidney is protected from damage. If this hypothesis proves to be correct, it may account for the great variation in the occurrence of the lower nephron syndrome after ischemic muscle trauma, depending on (a) the degree and duration of muscle ischemia and (b) the functional capacity of the liver.

Dunn and his coworkers,³⁰ while not questioning that other nephrotoxic substances obtainable from damaged muscle may be implicated, suggest that uric and phosphoric acid possibly play a part in the production of the renal lesions. Both of these acids are liberated in considerable amounts from severely injured muscle; and both, under experimental conditions, may produce lesions in the lower nephron.^{32,54}

In a recent paper⁶⁵ some proteolytic enzyme, set free or activated from damaged tissue, has been held responsible for the renal disturbances. In support of this hypothesis it was demonstrated that intraperitoneal injections of trypsin cause kidney lesions which are said to resemble strikingly those in human cases of crush injury or burns.

The mode of action of these various nephrotoxic agents released from damaged tissue is difficult to assess. Some may affect tubular cells directly; others may bring about primary renal vasoconstriction,^{21,47} and, in consequence, a state of anoxemia which is injurious to cells.

Part played by physicochemical alterations of blood

There is evidence that profound physicochemical alterations of the blood occur in some conditions that lead to lower nephron nephrosis. These alterations are mainly the result of destruction of tissue, and of excessive vomiting with dehydration. As to the former, considerable quantities of acid metabolites, such as lactate and phosphate, may be released. Absorption of these substances by the blood reduces the alkali reserve, causes an elevation of inorganic phosphate, and leads to acidification of the urine.¹⁶

Destruction of tissue or of blood will also set free intracellular potassium which has been locked up within cells. It is possible that the sudden liberation of excessive amounts may exert toxic effects.^{9,13}

Persistent vomiting leads to loss of chlorides and of water and to consequent upset of the physicochemical balance of blood and body fluids. This, in turn, causes diminution of kidney function. For example, it has been demonstrated that hypochloremia in man and experimental animals is commonly attended by a fall in glomerular filtration rate and extreme oliguria, despite normal fluid intake.^{50,89} The renal lesions observed in human cases of alkalosis (resulting from excessive vomiting or the taking of large quantities of sodium bicarbonate) are very similar to those in cases of the crush syndrome, excepting for the absence of heme casts.⁵⁵ Two such cases are included in the present series.

The mechanism by which physicochemical imbalance of body fluid brings about renal disturbances is conjectural.

Disturbances of renal blood flow. The role of shock

A cardinal prerequisite for normal function of the kidney is adequate circulation. Any measure which diminishes blood flow in the glomerular capillaries and which reduces pressure in these capillaries will lead to decreased filtration;⁷⁴ it will also lead to a diminished peritubular circulation and to reduction in essential oxygen supply.⁴⁰ There is a growing belief that renal ischemia, and consequently

anoxia, is of fundamental importance in the pathogenesis of the kidney disturbances with which we are concerned.^{20,23,49,57,60,70,77,82,83} The famous dictum of Haldane may aptly be applied here: "Anoxia not only stops the machinery but wrecks the machine."

The deleterious effects of inadequate circulation upon the kidney have been extensively studied in relation to shock. Although the hypotheses concerning shock are controversial, it seems to be established that deficit in the volume of circulating blood is an essential feature.^{84,88} It brings about regional vascular constriction as a compensatory mechanism. Now it has been demonstrated that blood flow in the kidney can vary independently of the general circulation.^{51,75,76,84} For example, when in shock the total circulating volume decreases to approximately one-half the normal value, the flow through the kidney decreases to one-tenth, one-twentieth, or even less.⁷⁵ The immediate effect is marked depression of urinary output, i.e. oliguria or anuria.^{51,68} The duration of ischemia is an important factor in determining renal injury.^{21,76,77,84} Thus van Slyke and his associates divide the effects of ischemia into three stages, depending on its duration: (1) reduced kidney function without damage to nephrons; (2) reversible damage to the nephrons, and (3) irreversible damage, with subsequent death from uremia. All three stages may occur in man.⁸⁴

The main factor held responsible for injury to the nephrons is renal anoxia.^{57,77,82}

Mechanism of oliguria

Three principal hypotheses have been advanced to account for the diminution in urinary output characteristic of lower nephron nephrosis: (1) Shut-down in renal circulation; (2) obstruction of tubules, and (3) unselective reabsorption of glomerular filtrate. The first of these hypotheses has already been referred to in the preceding sections; hence discussions will be confined to the two remaining.

Obstruction of tubules. That mechanical blockage of tubules with debris and heme masses is the deciding factor for oliguria and renal failure is the view put forth by Baker and Dodds⁴ and accepted by others.^{67,86} Most

investigators, however, do not share this hypothesis.^{3,12,16,26,28,30,40,46,56} Histologically, in many, perhaps in most, cases the number of tubules obstructed seems inadequate to cause renal impairment. To be sure, kidneys of lower nephron disease have not been studied in serial sections, and no quantitative determination of the extent of blockage has been made. Oliver⁶⁷ has recently stated that blockage becomes more evident when nephrons are dissected out in their entirety than in the usual sections. Nevertheless, on morphologic grounds the blockage hypothesis of oliguria is opposed (a) by finding little if any dilatation of the glomerular spaces and upper segments such as is to be expected when obstruction is complete; (b) by the fact that in many cases heme casts are scanty, and that they may even be absent.²⁸ On functional grounds, the criticism has been made that if blockage were the only factor concerned in the mechanism of oliguria, such urine as is passed should be of approximately normal composition, since it would be elaborated by unobstructed and presumably normal nephrons.^{15,16} But, usually analysis has shown that the urine has a low specific gravity, indicative of inadequate concentration of the glomerular fluid, and an abnormal composition. Some investigators regard tubular obstruction not as the cause but as the consequence of diminished renal function.^{12,40} It seems fair to conclude that mechanical blockage, while it may be a contributing factor, is in most cases not the primary cause of oliguria.

Unselective reabsorption of glomerular filtrate. Normally the renal tubules concentrate and otherwise modify daily about 150 liters of glomerular filtrate to 1.5 liters of urine through a process of selective reabsorption of water and of certain solutes. When the tubules become injured beyond a certain degree, their permeability is altered, and reabsorption becomes unselective. In other words, injury or death of tubular epithelium allows some of the unabsorbed glomerular filtrate to diffuse back into the blood of the peritubular capillaries. Any urine passed is relatively small in amount, of low specific gravity, and of abnormal composition.

Dunn and his coworkers were perhaps the

first to account for experimental oliguria on the grounds of tubular damage.^{31,32} Richards and his associates,⁷³ by direct microscopic observation of the living frog's kidney, confirmed Dunn's views. After poisoning frogs with a suitable dose of bichloride of mercury, and then examining the exposed kidneys of the living animals, it was found that glomerular circulation and filtration were extraordinarily active, and that the composition of the filtrate was approximately normal. But despite filtration of excessive amounts of fluid, no urine issued from the ureters: there was complete anuria. The only possible explanation is that because of loss of permeability (of the dead cells in the proximal tubules), the osmotic pressure of the blood in the peritubular capillaries is able to draw back all or nearly all of the glomerular filtrate. These experiments strengthen the hypothesis that tubular injury causes oliguria or anuria in lower nephron nephrosis. It will be recalled that portions of the lower segments show structural evidence of injury which varies from barely perceptible degeneration to frank necrosis. There can be little doubt that in the necrotic portion selective permeability of the tubular wall is abolished. It seems proper to assume that in earlier and less severe stages of the retrograde changes there also are alterations in cellular permeability. Unfortunately, the methods of the present-day do not permit us to determine such alterations. Perhaps it requires less extensive damage in the lower than in the upper segment to bring about oliguria, for when the glomerular filtrate reaches the lower segment it has already been considerably concentrated and modified.

Dunn and his associates³⁰ and others ascribe the oliguria of lower nephron disease to leakage of glomerular filtrate through the damaged tubular walls. As Bywaters and Dible¹⁶ state, this hypothesis fits best with histologic evidence. With these views we agree.

The role of extrarenal factors

It is generally believed that extrarenal factors may bring about a form of renal insufficiency which cannot be accounted for by morphologic changes in the kidneys. The main

clinical manifestations are, oliguria (or anuria) and azotemia. Among conditions in which extrarenal factors are held to operate are: excessive vomiting, dehydration, burns, profuse hemorrhage, trauma (including operative trauma) and shock.^{5,39} But these are precisely the conditions which may lead to the lower nephron syndrome. The histopathologic changes characteristic of this syndrome were until recent years unfamiliar. In discussing the pathogenesis it has been shown that several of the causal factors affect the kidney directly, either through vascular constriction with resulting ischemia and selective anoxia, or through primary injury of the lower segments.

It may well be that physicochemical imbalance of body fluids is of importance in bringing about renal failure.⁴⁰ But it seems necessary critically to reappraise the significance of various "extrarenal" factors in their relation to disturbances of kidney functions. In many cases, at least, renal insufficiency may be directly traced to faults within the kidney itself.⁵⁷

SUMMARY

(1) A syndrome characterized by oliguria (or anuria), heme pigment excretion, azotemia, hypertension, and uremia may develop in a variety of conditions associated with destruction of tissue (especially muscle) or intravascular hemolysis. Conditions in which this syndrome has been observed include: crushing injury and other forms of trauma to muscle, nontraumatic muscular ischemia, uteroplacental damage (and eclampsia), burns, transfusion with incompatible blood, black-water fever, and other types of intravascular hemolysis, heat stroke, sulfonamide intoxication, alkalosis, mushroom poisoning, and some other kinds of poisoning with vegetable and chemical agents. The mortality is high; death usually occurs within 10 days.

This syndrome has been the most frequent form of fatal kidney disorder encountered among military personnel during the war. The present communication is based upon the study of records and material from 538 fatal cases received at the Army Institute of Pathology.

(2) Specific lesions occur in the kidney. The essential changes are selectively restricted to the lower segments of the nephrons, and comprise: focal degeneration or necrosis, presence of heme casts, secondary inflammatory reactions in the surrounding stroma, and thrombosis of thin walled veins. The term lower nephron nephrosis is suggested as descriptive of the location and nature of the morphologic changes.

(3) The pathogenesis of the lesions has not yet been established. It is probable that several factors are concerned in combination. Among those implicated are: degradation products of myoglobin and hemoglobin, products of tissue breakdown, physiochemical alteration of blood and body fluids, shock and disturbances of renal blood flow resulting in ischemia of the kidney and anuria.

(4) The relation of symptoms to lesions is likewise incompletely known. It is probable that resorption of glomerular filtrate in injured segments plays a part in the development of renal insufficiency. But to a varying degree, at least, three other factors may also be of importance: mechanical blockage of the tubular lumens by casts, inadequate glomerular filtration, and disturbances of electrolyte balance of body fluids.

(5) It is apparent that present day information concerning this important renal syndrome is inadequate. It offers a promising field for clinical, morphological and experimental investigation.

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REFERENCES

- ¹ Anderson, W. A. D., Morrison, D. B., and Williams, E. F.: Pathologic changes following injections of ferrihemate (hematin) in dogs. *Arch. Path.* 33:589-602, 1942.
- ² Angevine, D. M., and Harman, J. W.: An analysis of a series of autopsies with hemoglobinuric nephrosis (Personal communication).
- ³ Ayer, G. D., and Gauld, A. G.: Uremia following blood transfusion, nature and significance of renal changes. *Arch. Path.* 33:513-532, 1942.
- ⁴ Baker, S. L., and Dodds, E. C.: Obstruction of the renal tubules during excretion of haemoglobin. *Brit. J. Exper. Path.* 6:247-260, 1925.
- ⁵ Bell, E. T.: *Renal Diseases*. Lea and Febiger, Philadelphia, 1946.
- ⁶ Green, H. N.: Shock producing factor(s) from striated muscle; I. Isolation and biological properties. *Lancet*, 2:147-153, 1943.
- ⁷ Bielschowsky, M., and Green, H. N.: Shock producing factor(s) from striated muscle; II. Fractionation, chemical properties and effective doses. *Lancet*, 2:153-155, 1943.
- ⁸ Bing, R. J.: The effect of hemoglobin and related pigments on renal functions of the normal and acidotic dog. *Bull. Johns Hopkins Hosp.* 74:161-176, 1944.
- ⁹ Birnbaum, W.: Crushing injuries with renal failure. *California & West. Med.* 64:15-18, 1946.
- ¹⁰ Blalock, A., and Duncan, G. W.: Traumatic shock, consideration of several types of injury. *Surg. Gynec. & Obst.* 75:401-409, 1942.
- ¹¹ Bott, P. A., and Richards, A. N.: Passage of protein molecules through glomerular membranes. *J. Biol. Chem.* 141:291-310, 1941.
- ¹² Brass, K.: Über ein charakteristisches Syndrom bei akuter schwerer Myolyse. *Frankfurt. Ztschr. f. Path.* 58:387-442, 1944.
- ¹³ Bywaters, E. G. L.: War medicine series; crushing injury. *Brit. M. J.* 2:643-646, 1942.
- ¹⁴ Bywaters, E. G. L., and others.: Discussion on effects on kidney of trauma to parts other than urinary tract, including crush syndrome. *Proc. Roy. Soc. Med.* 35:321-339, 1942.
- ¹⁵ Bywaters, E. G. L., and Beall, D.: Crush injuries with impairment of renal function. *Brit. M. J.* 1:427-432, 1941.
- ¹⁶ Bywaters, E. G. L., and Dible, J. H.: Renal lesion in traumatic anuria. *J. Path. & Bact.* 54:111-120, 1942.
- ¹⁷ Bywaters, E. G. L., Delory, G. E., Rimington, C., and Smiles, J.: Myohaemoglobin in urine of air raid casualties with crushing injury. *Biochem. J.* 35:1164-1168, 1941.
- ¹⁸ Bywaters, E. G. L., and Dible, J. H.: Acute paralytic myohaemoglobinuria in man. *J. Path. & Bact.* 55:7-15, 1943.
- ¹⁹ Bywaters, E. G. L., and Stead, J. K.: Production of renal failure following injection of solutions containing myohaemoglobin. *Quart. J. Exper. Physiol.* 33:53-70, 1944.
- ²⁰ Corcoran, A. C., and Page, I. H.: Effects of hypotension due to hemorrhage and of blood transfusion on renal function in dogs. *J. Exper. Med.* 78:205-224, 1943.
- ²¹ Corcoran, A. C., and Page, I. H.: Post-traumatic renal injury; summary of experimental observations. *Arch. Surg.* 51:93-101, 1945.
- ²² Corcoran, A. C., and Page, I. H.: Renal damage from ferroheme pigments, myoglobin, hemoglobin,

hematin. *Texas Rep. Biol. & Med.* 3:528-544, 1945.

²² Corcoran, A. C., and Page, I. H.: Genesis of crush syndrome. *J. Lab. & Clin. Med.* 30:351-352, 1945.

²⁴ Damon, S. R.: Food infections and Food Intoxications. Baltimore, Williams and Wilkins Co., 1928.

²⁵ Daniels, W. B., Leonard, B. W., and Holtzman, S.: Renal insufficiency following transfusion; report of 13 cases. *J. A. M. A.* 116:1208-1215, 1941.

²⁶ DeGowin, E. L., Warner, E. D., and Randall, W. L.: Renal insufficiency from blood transfusion, anatomic changes in man compared with those in dogs with experimental hemoglobinuria. *Arch. Int. Med.* 61:609-630, 1938.

²⁷ Darmady, E. M., and others.: Traumatic uraemia, reports on 8 cases. *Lancet*, 2:809-812, 1944.

²⁸ DeNavasquez, S.: Excretion of haemoglobin, with special reference to "transfusion" kidney. *J. Path. & Bact.* 51:413-425, 1940.

²⁹ Douglas, J. W. B.: Incidence of signs of renal injury following prolonged burial under debris in an unselected series of 764 air-raid casualties admitted to hospital. *Brit. J. Urol.* 17:142-147, 1945.

³⁰ Dunn, J. S., Gillespie, M., and Niven, J. S. F.: Renal lesions in 2 cases of crush syndrome. *Lancet*, 2:549-552, 1941.

³¹ Dunn, J. S., Haworth, A., and Jones, N. A.: Pathology of oxalate nephritis. *J. Path. & Bact.* 27:299-318, 1924.

³² Dunn, J. S., and Polson, C. J.: Experimental uric acid nephritis. *J. Path. & Bact.* 29: 337-352, 1926.

³³ Edwards, J. G.: The renal tubule (nephron) as affected by mercury. *Am. J. Path.* 18:1011-1027, 1942.

³⁴ Eggleton, M. G., Richardson, K. C., Schild, H. O., and Winton, F. R.: Renal damage due to crush injury and ischaemia of limbs of anaesthetized dog. *Quart. J. Exper. Physiol.* 32:89-106, 1943.

³⁵ Eggleton, M.: Crush kidney syndrome in the cat. *Lancet*, 2:208-210, 1944.

³⁶ Erb, I. H., Morgan, E. M., and Farmer, A. W.: Pathology of burns, pathologic picture as revealed at autopsy in series of 61 fatal cases treated at Hospital for Sick Children, Toronto, Canada. *Ann. Surg.* 117:234-255, 1943.

³⁷ Fahr, Th. in Henke, F., and Lubarsch, O.: *Handb. d. spez. path. Anat. u. Hist.*, Berlin, J. Springer, v. 6, pt. 1 & 2, 1925, 1934.

³⁸ Fairley, N. H.: Fate of extracorporeal circulating haemoglobin. *Brit. M. J.* 2:213-217, 1940.

³⁹ Fishberg, A. M.: Hypertension and nephritis. Philadelphia, 4th Ed. Lea and Febiger, 1939.

⁴⁰ Foy, H., Altmann, A., Barnes, H. D., and Kondi, A.: Anuria, with special reference to renal failure in blackwater fever, incompatible transfusions, and crush injuries. *Tr. Roy. Soc. Trop. Med. & Hyg.* 36:197-238, 1943.

⁴¹ Foy, H., Gluckman, J., and Kondi, A.: Pigment

metabolism and renal failure in acute sulphonamide haemolysis resembling blackwater fever. *Tr. Roy. Soc. Med. & Hyg.* 37:303-319, 1944.

⁴² French, A. J.: Hypersensitivity in the pathogenesis of the histopathologic changes associated with sulfonamide chemotherapy. *Am. J. Path.* 22:679-701, 1946.

⁴³ Gilligan, D. R., and Blumgart, H. L.: March hemoglobinuria; studies of clinical characteristics, blood metabolism and mechanism, with observations on 3 new cases, and review of literature. *Medicine*. 20:341-395, 1941.

⁴⁴ Gilligan, D. R., Altschule, M. D., and Katersky, E. M.: Studies of hemoglobinemia and hemoglobinuria produced in man by intravenous injection of hemoglobin solutions. *J. Clin. Investigation*. 20:177-187, 1941.

⁴⁵ Gollan, K. R., Lemberg, R., and Money, R. A.: Observations upon "crush injury" syndrome and Volkmann's contracture associated with severe brain injury and hyperthermia. *Med. J. Australia*. 2:212-214, 1945.

⁴⁶ Goodpastor, W. E., Levenson, S. M., and others.: Clinical and pathologic study of kidney in patients with thermal burns. *Surg. Gynec. & Obst.* 82:652-670, 1946.

⁴⁷ Goormaghtigh, N.: Vascular and circulatory changes in renal cortex in anuric crush-syndrome. *Proc. Soc. Exper. Biol. & Med.* 59:303-305, 1945.

⁴⁸ Gruber, G. B. in Henke, F., and Lubarsch, O. *Handb. d. spez. path. Anat. u. Hist.*, Berlin, J. Springer, v. 6, pt. 2, 1934 (refs. to hemoglobinuria in poisoning).

⁴⁹ Keele, C. A., and Slome, D.: Renal blood-flow in experimental "crush syndrome." *Brit. J. Exper. Path.* 26:151-159, 1945.

⁵⁰ Landis, E. M., Elsom, K. A., Bott, P. A., and Shiels, E.: Observations on sodium chloride restriction and urea clearance in renal insufficiency. *J. Clin. Investigation*. 14:525-541, 1935.

⁵¹ Lauson, H. D., Bradley, S. E., and Cournand, A.: Renal circulation in shock. *J. Clin. Investigation*. 23:381-402, 1944.

⁵² Luetscher, J. A., Jr., and Blackman, S. S., Jr.: Severe injury to kidneys and brain following sulfathiazole administration; high serum sodium and chloride levels and persistent cerebral damage. *Ann. Int. Med.* 18:741-756, 1943.

⁵³ Lund, C. C., Green, R. W., Taylor, F. H. L., and Levenson, S. M.: Burns, collective review. *Surg. Gynec. & Obst. (Intern. Abstr. of Surg.)* 82:443-478, 1946.

⁵⁴ McFarlane, D.: Experimental phosphate nephritis in rat. *J. Path. & Bact.* 52:17-24, 1941.

⁵⁵ McLetchie, N. G. B.: Renal lesions in case of excessive vomiting. *J. Path. & Bact.* 55:17-22, 1943.

⁵⁶ Macgrath, B. G., and Findlay, G. M.: Oliguria in blackwater fever. *Lancet*. 2:403-404, 1944.

⁵⁷ Macgrath, B. G., Havard, R. E., and Parsons,

D. S.: Renal syndrome of wide distribution induced possibly by renal anoxia. *Lancet*. 2:293-296, 1945.

⁵⁸ Malamud, N., Haymaker, W., and Custer, R. P.: Heat stroke. *MILITARY SURGEON*. 5:397-449, 1946.

⁵⁹ Mallory, T.: Personal communication.

⁶⁰ Mann, F.: Peripheral origin of surgical shock. *Johns Hopkins Hosp. Bull.* 25:205-212, 1914.

⁶¹ Mason, J. B., and Mann, F. C.: Effect of hemoglobin on volume of kidney. *Am. J. Physiol.* 98:181-185, 1931.

⁶² Millikan, G. A.: Muscle hemoglobin. *Physiol. Rev.* 19:503-523, 1939.

⁶³ Minami, S.: Über Nierenveränderungen nach Verschüttung. *Virchows Arch. f. path. Anat.* 245:247-267, 1923.

⁶⁴ Minett, F. C.: Haemoglobinurias and myoglobinurias of animals. *Proc. Roy. Soc. of Med.* 28:672-678, 1935.

⁶⁵ Mirsky, I. A., and Freis, E. D.: Renal and hepatic injury in trypsin "shock." *Proc. Soc. Exper. Biol. & Med.* 57:278-279, 1944.

⁶⁶ Moon, V. H.: Shock: Its Dynamics, Occurrence and Management. Philadelphia, Lea and Febiger, 1942.

⁶⁷ Oliver, J.: New directions in renal morphology: a method, its results and its future. *Harvey Lectures*, 40:102-155, 1945.

⁶⁸ Olson, W. H., Walker, L., and Necheles, H.: Study of anuria in experimental shock. *Proc. Soc. Exper. Biol. and Med.* 56:64-67, 1944.

⁶⁹ Page, I. H.: Occurrence of vasoconstrictor substance in blood during shock induced by trauma, hemorrhage and burns. *Am. J. Physiol.* 139:386-398, 1943.

⁷⁰ Page, I. H., and Abell, R. G.: State of vessels of mesentery in shock produced by constricting limbs and behavior of vessels following hemorrhage. *J. Exper. Med.* 27:215-232, 1943.

⁷¹ Parsons, C. G.: Traumatic uraemia. *Brit. M. J.* 1:180-182, 1945.

⁷² Paxson, N. F., Golub, L. J., and Hunter, R. M.: Crush syndrome in obstetrics and gynecology. *J. A. M. A.* 131:500-504, 1946.

⁷³ Richards, A. N.: Direct observations of change in function of the renal tubule caused by certain poisons. *Tr. A. Am. Physicians.* 44:64-67, 1929.

⁷⁴ Richards, A. N.: Croonian lecture: processes of urine formation. *Proc. Roy. Soc., London, s. B.* 126:398-432, 1938.

⁷⁵ Richards, D. W., Jr.: Circulation in traumatic shock in man. *Harvey lecture*, February 17, 1944. *Bull. New York Acad. Med.* 20:363-393, 1944.

⁷⁶ Scarff, R. W., and Keele, C. A.: Effects of temporary occlusion of renal circulation in rabbit. *Brit. J. Exper. Path.* 24:147-149, 1943.

⁷⁷ Selkurt, E. E.: Changes in renal clearances following complete ischemia of the kidney. *Federation Proc.* 4: 63, 1945.

⁷⁸ Shorr, E., Zweifach, B. W., and Furchgott, R. F.: On occurrence, sites and modes of origin and destruction, of principles affecting compensatory vascular mechanisms in experimental shock. *Science*. 102:489-498, 1945.

⁷⁹ Sobin, S. S., Aronberg, L. M., and Rolnick, H. C.: Nature of renal lesion with sulfonamides and its prevention with urea. *Am. J. Path.* 19:211-223, 1943.

⁸⁰ Starr, I. Jr.: Production of albuminuria by renal vasoconstriction in animals and in man. *J. Exper. Med.* 43:31-51, 1926.

⁸¹ Stoner, H. B., and Green, H. N.: Adenosine compounds and phosphates in blood of shocked rabbits. *J. Path. & Bact.* 66:343-354, 1944.

⁸² Tomb, J. W.: Anuria and anoxia. *J. Trop. Med.* 45:125, 1942.

⁸³ Tomb, J. W.: Crush injury and anoxia. *New Zealand M. J.* 42:75-77, 1943.

⁸⁴ Van Slyke, D. D., Phillips, R. A., Hamilton, P. B., Archibald, R. M., Dole, V. P., and Emerson, K., Jr.: Effect of shock on the kidney. *Tr. A. Am. Physicians.* 58:119-128, 1944.

⁸⁵ Vander Veer, J. B., and Farley, D. L.: Mushroom poisoning (mycetismus); report of 4 cases. *Arch. Int. Med.* 55:773-791, 1935.

⁸⁶ Wakeman, A. M., and others.: Metabolism and treatment of blackwater fever. *Am. J. Trop. Med.* 12:407-439, 1932.

⁸⁷ Walker, A. M., Bott, P. A., Oliver, J., and MacDowell, M. C.: Collection and analysis of fluid from single nephrons of mammalian kidney. *Am. J. Physiol.* 134:580-595, 1941.

⁸⁸ Wiggers, C. J.: Present status of shock problem. *Physiol. Rev.* 22:74-123, 1942.

⁸⁹ Wilkinson, B. M., and McCance, R. A.: Secretion of urine in rabbits during experimental salt deficiency. *Quart. J. Exper. Physiol.* 30:249-261, 1940.

⁹⁰ Young, J.: Renal failure after utero-placental damage. *Brit. M. J.* 2:715-718, 1942.

⁹¹ Yuile, C. L.: Hemoglobinuria. *Physiol. Rev.* 22:19-31, 1942.

⁹² Yuile, C. L., Gold, M. A., and Hinds, E. G.: Hemoglobin precipitation in renal tubules; a study of its causes and effects. *J. Exper. Med.* 82:361-374, 1945.

HEAT STROKE

A CLINICO-PATHOLOGIC STUDY OF 125 FATAL CASES*†

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(With fifty-eight illustrations)

INTRODUCTION

INCREASED attention has been directed to the harmful effects of heat during the recent war because of the numbers of troops suffering illness or death from exposure to unusual climatic factors.[‡] Heat disability falls into three categories: heat cramps, heat exhaustion, and heat stroke. *Heat cramps*, brought about mainly by a loss of body salt through sweating, is characterized by painful contractures of voluntary muscles, especially those of the extremities and the abdominal wall; the temperature is normal or slightly subnormal. *Heat exhaustion* covers a wide range of signs and symptoms. The temperature may be normal or subnormal but usually is slightly raised, and may reach 101°F. Ladell, Waterlow and Hudson,³¹ whose studies were carried on in Southern Iraq, observed that there were two types of heat exhaustion. One, occurring in the hottest weeks, was manifested chiefly by giddiness, anorexia, headache, cramps, vomiting, sweating, syncope on standing, evidences of dehydration, and oliguria. The other, occurring in the second half of the summer, was characterized by dizziness, exhaustion, anorexia, insomnia, dyspnea, decreased sweating, and polyuria, and frequently by "prickly heat." The first type they ascribed chiefly to salt depletion, the second to "a breakdown of the defense mechanism against heat," especially the mechanism of sweating. *Heat stroke* (or heat hyperpyrexia) usually comes on with dramatic suddenness but sometimes is

ushered in by premonitory symptoms. Its distinguishing features are defective sweating, delirium or coma, convulsive seizures, circulatory collapse, and a temperature of 106°F. or higher. When the temperature is between 103 and 106°F. the condition is spoken of as *borderline hyperpyrexia*. Although each of these categories may justifiably be regarded as a separate clinical entity, it is recognized that heat cramps may merge into heat exhaustion, and heat exhaustion into heat stroke.

"*Sunstroke*," a diagnosis rendered on some of the cases described in this paper, has been regarded by certain authors (e.g., Manson³²) as a distinct entity. Sunlight may contribute a heat load of considerable magnitude (Blum^{10,11}), but it is extremely doubtful that it plays a specific role in causing "stroke." Contrary to a rather prevalent belief, sunlight penetrates only a short distance into the body and does not directly affect the brain or meninges (Blum¹⁰). The experiments of Aron⁵ on monkeys show that heat stroke occurs not when sunlight impinges on the head alone, but when the whole body is exposed, indicating that the precipitating cause of the "stroke" is the total heat load, not the specific action of sunlight on the head.

This paper, based on a study of material received by the Army Institute of Pathology from military hospitals throughout the United States, is concerned primarily with heat stroke. Of the 125 fatal cases with which it deals there were 18 in which the temperature on admission to hospital was below 106°F., indicating that they belonged in the categories of heat exhaustion and borderline hyperpyrexia. In 9 of these, however, the temperature subsequently rose to hyperthermic heights, sometimes terminally. In 7 others a temperature of from 104 to 105°F. was recorded, and in the other 2, in which the course was of approxi-

* From the Army Institute of Pathology, Washington, D.C.

† Read before the meeting of the American Association of Neuropathologists, San Francisco, June 26, 1946.

‡ An outline of the historical aspects of heat stroke is to be found in the work of Wakefield and Hall.⁸⁸

mately 12 hours' duration, the temperatures were 97 and 101°F. respectively. The entire group has been analyzed as a single unit. It should be emphasized that none of our cases were characterized by dehydration and hemo-concentration. On the contrary, the patients appeared to be normal in these respects and some were actually hydremic.

MATERIAL AND METHODS

The material consisted of clinical records and autopsy protocols, together with fixed tissues and stained sections from 190 cases of heat stroke. Forty-three were not utilized for

TABLE I
AGE INCIDENCE OF 125 FATAL CASES OF HEAT STROKE

Age.....	18-25	26-30	31-38	39-41	Unknown
No. of Cases.	51	32	35	4	3

the study because of inadequate clinical information, and 22 were rejected because of significant intercurrent disease, particularly coronary sclerosis. The post-mortem examinations were performed by Army medical officers whose cooperation has made this study possible. Since the histories in some protocols were unduly brief, the statistical value of clinical data is to be regarded as only approximate.

Paraffin sections of all tissues stained with hematoxylin and eosin were available. Additional slides were prepared at the Army Institute of Pathology. Sections of heart from 70 cases were stained by the Bodian method, and for purposes of control a number were prepared with iron hematoxylin and fat stains. For the study of the central nervous system paraffin sections were stained routinely by cresyl violet, and in certain instances frozen sections were stained for fat by scarlet red, for myelin by the Spielmeyer method, and for axis cylinders by the Bodian method. Celloidin embedding was done in selected cases.

INCIDENCE

A general idea of the incidence of heat disability in armed forces may be gained from three sources: Steinhausen,⁵² who states that in

the Prussian Army between 1895 and 1904 there were 449 cases with a mortality of 11.6 per cent; Wakefield and Hall,⁵³ who cite 2,049 cases with a mortality of 0.07 per cent in the United States Navy between the years 1911 and 1926; and Wallace,⁵⁹ who during one summer at Keesler Field, Mississippi, observed 99 cases of which 4 were severe. The present series of 125 apparently comprises the largest number of instances of fatal heat stroke studied, but its ratio to the group in which recovery followed heat disability in the United States Army is unknown to us.

In civilian life heat stroke has, as a rule, been reported in individuals of advanced age, who frequently had cardiovascular and other disorders. Our material, on the other hand, is from the military age group (Table I), and includes only those cases in which post-mortem examination revealed no physical abnormality which could not be attributed to heat stroke.

Of the 125 soldiers who sustained fatal heat stroke, 120 were of the white race, 4 Negro and 1 Indian. They ranged in military rank from privates to captains, the ratio of enlisted men to officers being approximately 8:1.

The disorder was most often reported in

TABLE II
LOCATION OF CAMPS WHERE FATAL HEAT STROKE OCCURRED, AND THE RESPECTIVE INCIDENCE

State	No. of Cases
Texas.....	28
Georgia.....	17
Mississippi.....	14
Florida.....	12
Virginia.....	11
Louisiana.....	10
California.....	9
Alabama.....	7
Missouri.....	5
North Carolina.....	4
Kentucky.....	2
Arkansas.....	2
Kansas.....	1
Tennessee.....	1
Oklahoma.....	1
South Carolina.....	1
Total.....	125

and around military camps in the southern United States. The incidence in relation to location of the camps is shown in Table II. While the distribution may be proportional to the number of troops in the respective states, it probably also bears a relationship to climatic conditions in these geographic areas. Heat stroke always took place from May to September inclusive, with the peak incidence in July. The highest number of cases seen in a year was in 1943 when, presumably, the largest number of troops were undergoing intensive training (Table III).

ETIOLOGIC FACTORS

Heat as the direct etiologic factor in heat stroke has been established through clinical studies (Adolph,¹ Bazett *et al.*,⁶ Bean and Eichna,⁷ Castellani,¹² Weiner⁶²) and has been confirmed experimentally in animals (Hall and Wakefield,²³ Hartman and Major,²⁴ Marsh³⁸). The exact environmental conditions of temperature, humidity, wind velocity, and movement of air, as well as accessory factors such as strenuous muscular exercise and unsuitable clothing are well known. In 118 of our 125 cases there was a history of exposure to sun under conditions of high environmental temperature; in 3 heat stroke occurred in pursuance of kitchen or ward duty, while in the remaining 4 cases no information bearing on environmental factors is available. The great majority of the patients were engaged in some form of military exercise, such as long marches,

TABLE III
INCIDENCE OF FATAL HEAT STROKE BY
MONTH AND YEAR

Month	No. of Cases	Year	No. of Cases
May.....	5	1941.....	1
June.....	23	1942.....	33
July.....	59	1943.....	71
August.....	29	1944.....	20
September.....	9		—
Total.....	125	Total.....	125

drill, or target practice. Usually the "stroke" occurred during activity but sometimes it set in hours later. Data on the weather conditions at the camps at which our cases occurred and the conclusions as to the etiologic significance of dry and wet bulb temperatures, wind velocity, and other factors are being presented in a separate paper (Schickele⁴⁸).

Lack of acclimatization has long been regarded as one of the chief factors leading to heat stroke. In our series it seems to have played an important role (Table IV). Approximately one-fourth of the men had been in their respective camps for less than 2 weeks and about one-half for less than 2 months when heat stroke occurred. The majority had not previously been in any other camp in the South, nor more than 2 months in the Army. It should be emphasized that susceptibility to heat may have been as decisive a factor as lack of acclimatization in the production of heat

TABLE IV
DATA DEALING WITH THE FACTOR OF ACCLIMATIZATION IN 125 FATAL CASES OF HEAT STROKE

Length of Duty in Camp at which Death Occurred	No. of Cases	Length of Continuous Duty in the South							Total Length of Time in Service						
		1-2 wks.	2-4 wks.	1-2 mths.	2-6 mths.	6-12 mths.	1-2 yrs.	2-5 yrs.	1-2 wks.	2-4 wks.	1-2 mths.	2-6 mths.	6-12 mths.	1-2 yrs.	2-5 yrs.
1-2 wks.	46	34	4	0	3	3	1	1	11	24	0	1	2	4	4
2-4 wks.	22	0	16	1	3	1	1	0	0	9	8	3	1	1	0
1-2 mths.	16	0	0	12	1	1	2	0	0	0	10	1	3	2	0
2-6 mths.	33	0	0	0	25	6	1	1	0	0	0	20	7	3	3
6-12 mths.	6	0	0	0	0	5	1	0	0	0	0	0	6	0	0
1-2 yrs.	2	0	0	0	0	0	1	1	0	0	0	0	0	0	2

TABLE V
DISTRIBUTION OF CASES ACCORDING TO THE
DURATION OF ILLNESS

Duration	No. of Cases	
Less than 24 hours.....	63	(70%)
From 24 to 48 hours.....	12	(30%)
From 2 to 12 days.....	15	
No. of Cases of Known Duration....	90	
No. of Cases of Unknown Duration..	35	
Total.....	125	

stroke; however, there was a history of previous intolerance to heat in only 5 instances. It is significant that most of the patients were somewhat overweight or actually obese. There are too few data to allow an evaluation of alcohol consumption as a predisposing factor.

CLINICAL FEATURES

COURSE. There were three types of onset: a) acute, without apparent warning (71 per cent), b) relatively acute, with brief prodromal symptoms lasting minutes to hours (21

per cent), and c) insidious, with premonitory signs and symptoms lasting sometimes for several days (8 per cent). The manifestations during the prodromal period, in the order of their frequency, were faintness, staggering gait, dizziness, headaches, nausea and vomiting, purposeless movements, muscle cramps, choking, difficulty in swallowing or speaking, numbness of extremities, drowsiness, restlessness, mental confusion, dryness of the mouth, excessive thirst, anorexia, and diarrhea.

Data on the duration of illness reveal that death occurred in less than 24 hours in approximately 70 per cent of the cases, and in from 1 to 12 days in the remaining 30 per cent (Table V). The statement frequently made in the literature, that if patients with heat stroke survive the first 24 hours they usually go on to complete recovery, obviously needs modification.

Variation in the clinical course was related to the duration of the illness (Table VI). When death occurred in less than 48 hours early coma or delirium persisted until death. When the illness lasted longer than 48 hours, the course was characterized either by early

TABLE VI
TYPES OF CLINICAL SYNDROME AND THE DURATION OF ILLNESS IN 90 FATAL CASES OF HEAT STROKE

Syndrome	Survival Time		
	Less than 24 hrs.	24 to 48 hrs.	2 to 12 days
Acute Onset with Early Persistent Coma or Delirium.....	63	9	0
Acute Onset with Early Coma or Delirium, but with Remission and Late Relapse.....	0	3	8
Insidious Onset with Progressive Course and Late Development of Coma...	0	0	7

TABLE VII
TEMPERATURE LEVELS, PULSE RATES AND RESPIRATORY RATES ON ADMISSION TO HOSPITAL

Temperature	No. of Cases	Pulse Rate	No. of Cases	Resp. Rate	No. of Cases
97 to 99.....	3	100 to 130.....	13	10 to 20.....	1
99 to 103.....	3	130 to 160.....	23	20 to 30.....	4
103 to 106.....	12	160 to 200.....	24	30 to 60.....	31
106 to 111.....	107				
Total.....	125	Total.....	60	Total.....	36

coma which tended to clear up partially until a terminal relapse supervened, or by slow progression and late coma.

TEMPERATURE, PULSE, RESPIRATION AND BLOOD PRESSURE. The temperatures on admission to hospital ranged from 99 to 111°F. in all except 3 cases, the elevation being 106° or higher in 85 per cent (Table VII). (Most of the temperatures were rectal or axillary.) In the cases in which subnormal or slightly elevated temperatures were recorded, there was usually a subsequent rise to hyperthermic levels (Fig. 1A). Initially high temperatures were often reduced by ice packs and other cooling measures, sometimes to subnormal levels, but as a rule there was a secondary rise (Fig. 1B) and, in cases of long duration, several rises (Fig. 2). Peripheral vasoconstriction produced by cold, hindering the escape of heat through the skin, may account for the initial secondary rise in temperature, but the subsequent fluctuations suggest a persistent disturbance in thermoregulation.

Elevations in pulse and respiratory rates were usually of the same relative degree, and corresponded to the rise in temperature. The pulse rates varied from 100 to 200 per minute, being above 130 in approximately 80 per cent of the cases. The pulse was more often rapid

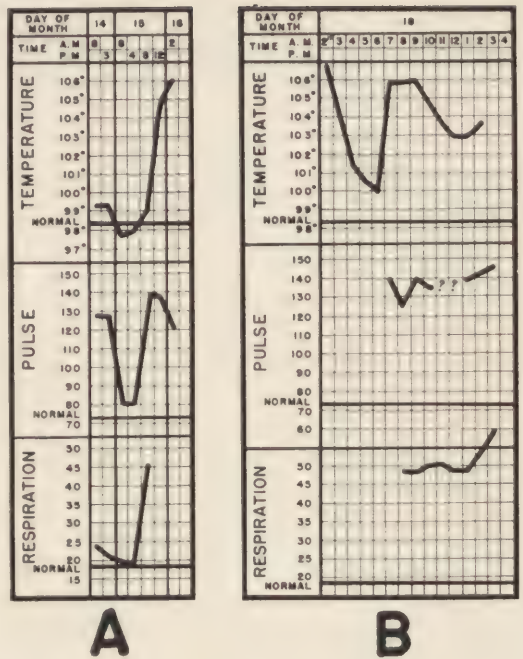


FIG. 1. Temperature, pulse, and respiration curves in two fatal cases of heat stroke. In A (AIP Acc. 102705) the temperature fell to a subnormal level before hyperthermia set in; in B (AIP Acc. 116302) the high temperature on admission was reduced by therapeutic measures, but hyperthermia again developed.

and thready than full and bounding. The respiratory rate was usually increased, being

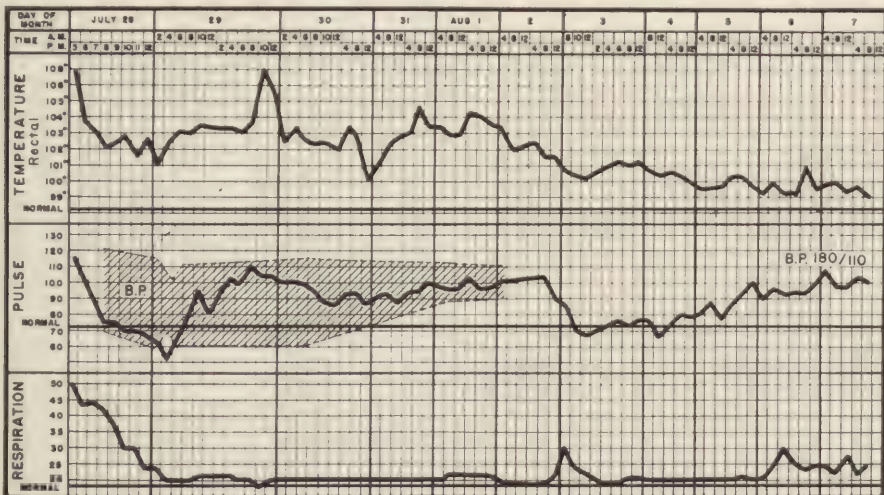


FIG. 2. Temperature, pulse, and respiration curves in a case in which hyperthermia persisted despite treatment (AIP Acc. 120161). Frequent fluctuation of the curves was a characteristic finding in the more protracted cases of heat stroke.

TABLE VIII
BLOOD AND PULSE PRESSURES ON ADMISSION TO HOSPITAL IN 55 FATAL CASES OF HEAT STROKE

Systolic		Diastolic		Pulse Pressure	
Mm. Hg.	No. of Cases	Mm. Hg.	No. of Cases	Mm. Hg.	No. of Cases
40 to 80.....	19	0 to 30.....	26	90 to 130.....	10
80 to 100.....	14	30 to 60.....	10	50 to 90.....	27
100 to 130.....	18	60 to 90.....	16	30 to 50.....	15
130 to 150.....	4	90 to 100.....	3	20 to 30.....	3

above 30 per minute in 86 per cent of the cases; breathing was often of the Kussmaul type, except in terminal stages when it generally took on a Cheyne-Stokes character.

In 55 cases in which the blood pressure readings on admission to the hospital were available (Table VIII) the systolic pressure ranged from 40 to 100 mm. Hg. in 60 per cent, the diastolic pressure from 0 to 60 mm. in 65 per cent, and the pulse pressure from 50

to 130 mm. Hg. Thirty-five per cent of the 55 had normal or slightly elevated blood pressure readings.

SYMPTOMS. A survey of the symptoms (Table IX) reveals that virtually all systems were affected. Three fundamental types of disturbances were evident: 1) symptoms regarded as directly related to the hyperthermia, therefore primary, 2) symptoms characteristic of shock, and 3) complications arising from chemical and pathologic changes.

Among the primary symptoms, those relating to the nervous system were outstanding. Disturbances in consciousness in the form of coma, stupor, or delirium were almost constant features, while convulsions, either generalized or Jacksonian in type, occurred in approximately 60 per cent of the cases. Pupillary changes and exaggeration or suppression of tendon reflexes were common but were not tabulated, since in most instances they were regarded as concomitants of stupor or coma. Damage to the central nervous system was manifest from the onset and persisted to the end; in the cases of longer duration dementia, aphasia, or hemiplegia indicated that the effect on the nervous system was probably lasting and irreversible. A direct relationship between the nervous manifestations and the degree and duration of hyperthermia was always evident. Disturbances in sweating likewise were intimately related to the hyperthermia, most commonly in the form of suppression; in a few instances, however, there was hyperhidrosis. Rarely was there the cold clammy skin observed in shock. In none of the cases was

TABLE IX
SIGNS AND SYMPTOMS IN 125 FATAL CASES OF HEAT STROKE, IN ORDER OF FREQUENCY

Signs & Symptoms	No. of Cases
Coma.....	116
Cyanosis.....	90
Disturbances of Sweating.....	88
Suppression.....	70
Excess.....	11
"Clammy Skin".....	7
Convulsions.....	77
Râles.....	58
Incontinence.....	48
Vomiting.....	47
Bleeding (Skin & mucous membranes)....	46
Delirium or Stupor.....	33
Disturbances of Muscle Tone.....	32
Rigidity.....	20
Flaccidity.....	8
"Cramps".....	4
Pos. Kernig & Brudzinski.....	16
Pyramidal signs.....	12
Opisthotonos.....	7
Tetany.....	7
Diarrhea.....	5
Anuria.....	4
Hematuria.....	3
Jaundice.....	3
Decerebrate Rigidity.....	2

"prickly heat" described. Defective sweating has long been recognized as an early manifestation of heat stroke (Willcox⁶⁵). According to Ladell, Waterlow and Hudson,³¹ whose work was done on nonfatal cases in Southern Iraq, virtually all patients with heat stroke had a suppression of sweating, whereas in heat exhaustion occurring in the hottest weeks the great majority (87 per cent) exhibited profuse sweating. The suddenness of the suppression of sweating in heat stroke and its prompt restoration on treatment, together with the absence of "prickly heat" or other condition of the skin which could be held accountable, led Ladell and his associates to believe that the first breakdown in heat stroke is in the sweating mechanism, in that part of the mechanism which is located in the central nervous system.

Certain symptoms were present which in all respects were similar to those seen in shock. Foremost among these were pallor or slight cyanosis, vomiting, fall in blood pressure, a rapid and thready pulse, and shallow and sighing respiration. In contrast to the symptoms resulting from hyperthermia, those of shock were inconstant: they occurred at any stage of the disorder, often were reversible, and their severity generally did not correspond to the degree of temperature elevation. Other symptoms which may have been related to shock were those of diarrhea and oliguria, the latter doubtless being more common than the records indicated. The degree of fall in blood pressure was taken as the most satisfactory, although admittedly an undependable, criterion of the presence of shock (Moon,^{37,38} Wright and Devine⁶⁹). (The pulse pressures were too variable to serve as a reliable index of shock.) In our cases the presence or absence of shock rather than the degree of hyperthermia, was the best prognostic index since it was on this factor that the ultimate outcome usually depended. Thus, in cases in which survival was longest, shock was either successfully controlled at the very outset or was not appreciable until the terminal stages.

Among the complications during the course of heat stroke were muscle cramps and tetany, which may be ascribed to hypochloremia and

alkalosis respectively. Pneumonia, uremia, hematuria, and jaundice were observed, especially in cases of longer duration.

LABORATORY STUDIES

BLOOD CELLS. Blood counts made during the early stages of heat stroke revealed in 22 of 32 cases a leukocytosis ranging from 10,000 to 28,950 cells per cmm.; leukocyte values in cases of longer duration were not listed because of the prevalence of complicating factors such as pneumonia (Table X). As a rule the

TABLE X

THE BLOOD LEUKOCYTE VALUES IN CASES OF HEAT STROKE FATAL IN LESS THAN 48 HOURS. ONLY UNCOMPLICATED CASES ARE INCLUDED

Duration of Illness	W.B.C. (per cmm.)		
	5 to 10,000	10 to 18,000	18 to 28,950
Less than 24 hrs.	10	9	8
From 24 to 48 hrs. ...	0	3	2
Total	10	12	10

differential count was within normal limits when the total was not greatly altered. Leukocytosis was due largely to an increase in neutrophils. These figures confirm the observations of Gauss and Meyer¹⁹ in a group of 25 cases of heat stroke.

Red blood cells and hemoglobin were within normal limits except for a few cases in which a decrease of both was observed, and several others in which the erythrocytes rose to polycythemic levels (Table XI). In only 1 of 15 cases was there an elevation in the hematocrit value and this was slight. Various investigators (Heilman and Montgomery,²⁵ Chakravarti and Tyagi,¹³ Wilcocks⁶⁴) have reported increases in viscosity, specific gravity, red and white blood counts and percentage of hemoglobin—findings which suggest that hemoconcentration occurs in heat stroke. However, with the exception of leukocytosis, which is probably due simply to accelerated circulation, we have been unable to confirm the existence of hemoconcentration as a regular feature.

TABLE XI
RED BLOOD CELL, HEMOGLOBIN AND HEMATOCRIT VALUES IN FATAL HEAT STROKE

R.B.C. (in millions) (Normal: 4.6 to 6.2) Values		Hemoglobin (in %) (Normal: 90 to 110) Values		Hematocrit (in % packed cells) (Normal: 45 to 47) Values	
No. of Cases		No. of Cases		No. of Cases	
3.42 to 4.00.....	3	45 to 75.....	1	35 to 45.....	9
4.00 to 4.60.....	15	75 to 90.....	15	45 to 47.....	5
4.60 to 6.20.....	15	90 to 110.....	12	50.....	1
6.20 to 6.89.....	2	110 to 130.....	3		—
	—		—		—
Total.....	35	Total.....	31	Total.....	15

TABLE XII
PROTHROMBIN TIME, PLATELET COUNT AND BLEEDING TIME IN 10 FATAL CASES OF HEAT STROKE

AIP Acc.	Duration of Ill- ness (Hrs.)	Prothrombin Time (Sec.) (Control: 14-19 Sec.)		Platelet Count (Normal: 200,000-500,000)		Bleeding Time (Min.) (Normal: 1-5 Min.)	
		On Ad- mission	Subsequent Times	On Ad- mission	Subsequent Counts	On Ad- mission	Subsequent Times
113894*	5	15	—	—	—	—	—
112746*	6	30	—	—	—	—	—
117740*	7	16	17 (4th hr.)	120,000	—	—	—
120158	8.5	—	—	56,000	—	—	—
118077*	12	16	20 (6th hr.)	104,000	40,000 (6th hr.)	—	—
107487	20	—	—	—	—	3.5	—
107486	22	—	—	22,300	—	3.5	—
97556	47	—	11 (8th hr.)	—	—	—	—
94751	60	51	49 (2d day) 108 (2d day)† 72 (3d day)	—	90,000 (2d day)† 70,000 (3d day)	—	10 (2d day)† —
118078*	276	16	20 (6th hr.) 18 (2d day) 14 (3 day)§ — — — — — 16 (12th day)	108,000	92,000 (6th hr.) 44,000 (2d day) 31,000 (3d day)§ 78,000 (4th day) 66,000 (5th day)¶ 168,000 (6th day) 94,000 (7th day) 130,000 (8th day) 178,000 (9th day) 140,000 (10th day) 260,000 (12th day)	—	4.8 (2d day) — 3.0 (3d day)§ — 6.0 (5th day)¶ 6.2 (6th day) 6.0-8.0

* The prothrombin and platelet studies done on these cases were reported by Wright, Reppert and Cuttino(see References).
† These determinations were made six hours after parenteral administration of 5.0 mg. of vitamin K.
§ Values shortly after transfusion of 400 cc. of whole blood.
¶ Subsequently on the same day a transfusion of 500 cc. of whole blood was given.

COAGULATION MECHANISM. Platelet counts were performed in 6 cases (Table XII) and all indicated a reduction in number. Generally the fall was progressive, but in one instance (Case 118078) in which survival was unusually long there was a return to a normal value before death. The prothrombin time, on the other hand, was within normal range except in one (Case 94751) in which it was much prolonged. The bleeding time

reduced in number, in 3 the prothrombin time was normal on admission but was definitely prolonged during the subsequent course, and in 3 the bleeding time also was prolonged in the later stages.* Prolongation of prothrombin time and reduction in platelets have been observed also by Wilson and Doan⁶⁷ in patients subjected to artificially induced fever.

BLOOD CHEMISTRY. Elevation in nonprotein nitrogen of the blood was moderate in

TABLE XIII
NONPROTEIN AND UREA NITROGEN VALUES IN 21 FATAL CASES OF HEAT STROKE

AIP Acc.	Duration of Illness (Hrs.)	Blood Pressure	Blood or Plasma Transfusion	Nonprotein Nitrogen (Normal: 15 to 40 mg. %)	Urea Nitrogen (Normal: 8 to 15 mg. %)
120160	3	70/0, 90/50	+	—	25.3
101829	7.5	80/40, 100/60, 96/50	0	24.6	14.2
98083	8	150/90	0	53.4	18.0
120158	8.5	120/0, 110/40, 60/0	+	—	19.0
99511	9	52/0, 96/50, 105/85	+	40.0	—
98258	11	60/20, 110/70, 60/40	0	52.3	—
116302	15	100/40	+	—	14.1
98086	15	60/20, 110/30, 90/0	0	57.0	22.0
99261	16	84/50, 80/60	0	60.0	—
120159	18	80/0, 140/80, 80/60	0	—	13.9
114215	19	90/70, 90/50, 120/70	0	45.0	—
99112	21	130/80	+	66.0	28.0
97555	26	60/40, 110/70, 60/40	+	45.0	—
86617	32	80/60	0	—	17.0
97554	34	136/80, 86/40	+	48.0	—
97148	35	150/110, 60/40	0	58.0	—
115686	39	135/65, 130/90	0	49.0	—
97556	47	80/50, 100/70, 135/85	+	43.0	—
94751	60	125/70, 108/60	+	51.0	20.0
115309	132	142/30, 82/52, 100/80	0	48.0	8.6
120161	249	100/60, 114/60, 110/90	+	130.0-229.0	25.9-46.8

was found to be slightly or moderately increased. The clotting time in 2 instances (Cases 107486 and 107487) was within normal limits, and in one (Case 120158) was found to be 45 minutes; in this case it was noted that for many minutes after a transfusion had been given blood continued to ooze from the puncture wound. Most of these observations are in accord with those of Wright, Reppert and Cuttino⁷⁰ in 6 nonfatal cases of heat stroke; in all instances the platelets were

all except one of 21 samples, with values ranging from 40 to 229 mg. per cent (Table XIII). Blood urea nitrogen, on the other hand, was less elevated, the levels being 17 to 46.8 mg. per cent. These findings were just

* The figures of Wright and his associates showed a maximum deviation from normal varying from 30,000 to 85,000 per cmm. for platelets, from 17 to 38 sec. for prothrombin time, and from 3 to 12 min. for bleeding time.

as evident in cases of a few hours' standing as in those of longer duration, and just as marked with or without blood transfusion. Similar findings have been reported in clinical cases (Chakravarti and Tyagi,¹³ Wallace,⁵⁹ Wilcocks⁶⁴) as well as in experimental heat stroke in animals (Hall and Wakefield,²³ Marsh³³). The changes have been attributed by Hall and Wakefield to rapid destruction of proteins resulting from hyperthermia; by Marsh, to renal damage, and by Chakravarti and Tyagi, to both. That destruction of proteins may be a contributing factor in azotemia is suggested by the discrepancy in nonprotein and urea nitrogen values.

The validity of an actual increase in the urea nitrogen is open to some question, however, inasmuch as Ladell, Waterlow and Hudson³¹ found the blood urea of fit soldiers in Southern Iraq to average 47.5 mg. per cent (normal: 20-30 mg.). In view of the fact that the daily temperature was more than 115°F. during the week their study was made, it seems unlikely that the nonprotein and urea nitrogen levels could have been that high in the normal soldier in southern U.S.A. It is also of interest that, according to their norm, Ladell, Waterlow and Hudson found no elevation of blood urea in cases of nonfatal heat stroke, but a substantial rise (average of 103 mg. per cent) in non-fatal heat exhaustion.

As to the factor of renal damage, microscopic examination frequently revealed lower nephron nephrosis in early stages of heat stroke (see section on pathology). It would seem therefore that altered functional activity of the kidneys may also play a role in the accumulation of nitrogenous products in the blood. In cases of longer duration in which renal damage was more severe, the increase in both nonprotein and urea nitrogen was much greater and was associated with symptoms of uremia.

The CO₂ combining power was definitely reduced in the 16 cases in which the values are known, ranging from 19.6 to 46.0 volumes per cent, with an average of 33. In the absence of a record of the pH of the blood this change is difficult to evaluate; it is in keeping, how-

ever, with reports in the literature which state that high blood lactic acid and low CO₂ combining power are characteristic findings in heat stroke. The fall in CO₂ combining power of the blood has been regarded as evidence of alkalosis due to hyperventilation, an interpretation which seems plausible in light of the development of symptoms of tetany in some of our cases, in one of which the CO₂ combining power was 19.8 volumes per cent.

The blood chlorides ranged from 231 to 804 mg. per cent (as NaCl), being lower than 600 mg. per cent in 27 of 31 cases. These figures are not open to evaluation, however, since the majority of the patients received saline solution intravenously. In a study of 20 nonfatal cases of heat disability occurring among troops in the desert of Arizona, Rosenbaum⁴⁶ was unable to demonstrate a definite hypochloremia but the possibility of a relative salt deficiency in the tissues could not be excluded.

The nature of these complex chemical changes is obscure. Similar findings have been reported in shock. Moon^{37,38} has emphasized the frequency with which electrolytic disturbances, elevation of nonprotein nitrogen, and reduction of alkali reserve of the blood occur in shock. Hemoconcentration also has been regarded by him as a characteristic feature of shock, but other investigators have shown that either hemoconcentration or hemodilution may obtain, depending on the cause of the shock (Cournand *et al.*,¹⁴ and Richards⁴⁵). According to Ladell, Waterlow and Hudson,³¹ hemodilution, as manifested by low hemoglobin and diminution of chloride content of the blood, is usual in the later stages of nonfatal heat stroke, because water accumulates in the body upon the suppression of sweating. A tendency toward hemodilution was noted also in our cases.

URINE. Urinalyses were rarely done, so that our information is limited to the fact that albuminuria, hematuria and casts were found in cases of longer duration. In every one of 25 cases of heat stroke studied by Gauss and Meyer¹⁹ the urine contained hyaline and granular casts, in 5, albumin, and in 20, pus cells.

SPINAL FLUID. The pressure was increased

in 2 cases of the 24 in which spinal fluid was examined, and the fluid was blood-tinged in 7.

ELECTROCARDIOGRAPHY. In the few cases in which electrocardiographic determinations were made the records suggested "toxic" damage to the myocardium (Fig. 3). Repeated

July 20, 1943. During that day he had participated in routine military exercises, and apparently was well until 5:45 P.M. when he suddenly collapsed and became unconscious. In hospital 15 minutes later he became delirious. The temperature was 109°F., pulse 128, respiration 36, and blood pressure 80/0 mm.

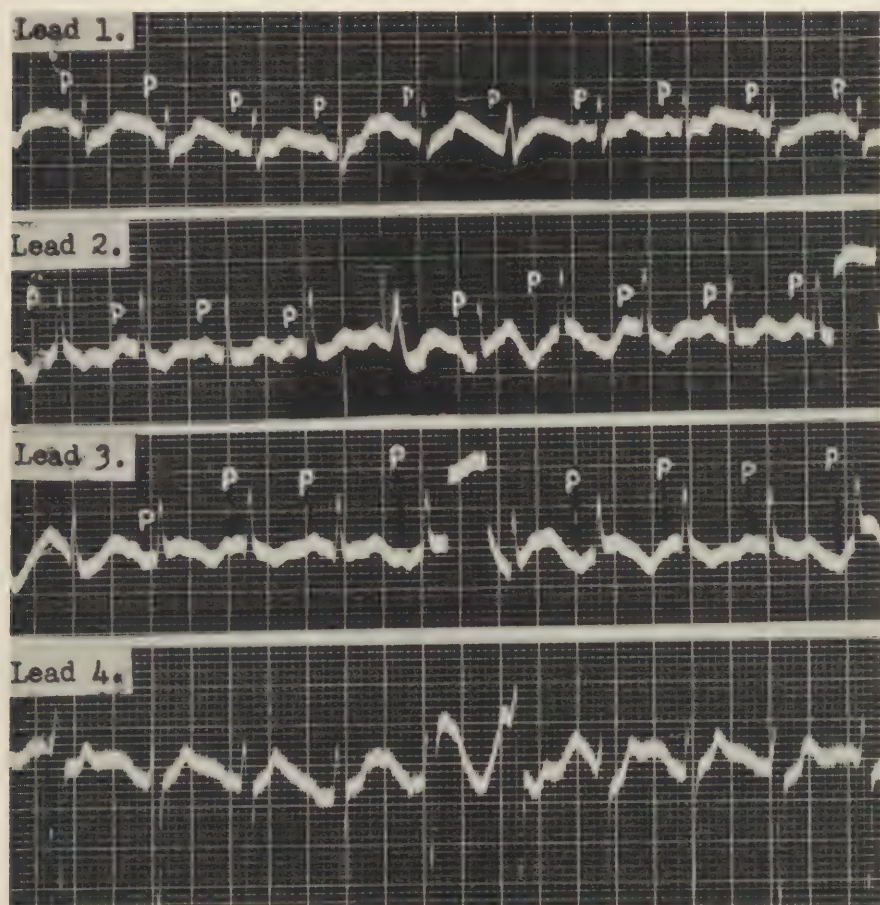


FIG. 3. Electrocardiogram of a comatose patient with a temperature of 109°F. (AIP Acc. 98083). There is a regular rhythm with changing pace maker. P-2 and P-3 deviate from upright to inverted; QRS complexes vary somewhat in height, and T-1 is diphasic while T-2 and T-3 are inverted to upright. The changes suggest an advanced toxic process in the myocardium.

electrocardiograms in one case indicated that the abnormalities were transient.

ILLUSTRATIVE CASES

I. Acute Onset of Early and Persistent Coma or Delirium.

AIP Acc. 97599. A white male, aged 37, was admitted to a hospital in Louisiana on

Hg. The skin was hot and dry, and there were scattered petechial hemorrhages over the chest and abdomen. Coma soon set in. Repeated generalized convulsions occurred. The treatment consisted of ice packs, cold enemas, and exposure to an electric fan. Death occurred at 7:53 P.M., approximately 2 hours after the onset.

AIP Acc. 99112. A white male, aged 22, was admitted to a hospital in North Carolina at 6:25 P.M. on June 17, 1943. During a four-mile hike in the afternoon, he had complained of excessive thirst, and about 4:30 P.M. he collapsed, became delirious and incontinent of urine and feces. He was in deep coma, the pupils were dilated and nonreactive, the skin hot and dry, the muscles hypertonic, and the knee jerks unobtainable. The temperature was 109°F., pulse 120, blood pressure 120/80 mm. Hg. Blood studies yielded the following results: red blood cells, 4,900,000; hemoglobin, 90 per cent; white blood cells, 28,050; nonprotein nitrogen, 66 mg., urea nitrogen, 28 mg., chlorides, 410 mg. per cent; and CO₂ combining power, 31.9 volumes per cent.

The temperature was reduced to 102.6°F. by means of an ice water spray and exposure to electric fans. The patient also received 1000 cc. of 5 per cent glucose in saline intravenously. On being placed in an oxygen tent he seemed to respond slightly, the pulse being of good volume and respirations numbering 24 per minute. Soon, however, he lapsed into a wild delirium which abated when paraldehyde was administered by rectum. Intravenous saline solution again was given, but coma supervened and death occurred at 1:41 P.M., approximately 21 hours after onset.

AIP Acc. 97554. A white male, aged 19, was admitted to a hospital in Georgia at 1:20 P.M. on July 23, 1943. He had been on a march that morning when at 11:00 A.M. he suddenly staggered and fell. Shortly thereafter he became unconscious and incontinent of urine and feces. His axillary temperature was 107°F. On examination the patient was comatose, the rectal temperature was 109°F., the blood pressure 136/80 mm. Hg., the skin hot and dry, the pupils pin-point and poorly reactive, and the tendon reflexes unobtainable. Treatment consisted of ice water baths and enemas, alcohol sponges, and infusion with 5 per cent glucose in saline. The temperature fell to 98°F. but soon rose to 101°F. The limbs became spastic, and the Babinski sign was elicited bilaterally. Convulsive seizures occurred. The breathing was stertorous, and

there was bloody expectoration. The patient then received 20 cc. of 50 per cent glucose and 10 cc. of calcium gluconate intravenously. Shortly afterward he was given a transfusion of 1500 cc. of plasma, but he remained comatose. Cardiac stimulants were to no avail. The temperature fluctuated between 101 and 104°F., the blood pressure fell to 86/64 mm. Hg., there was increasing cyanosis and the pulse became rapid and thready.

Blood studies yielded the following results: red blood cells, 4,320,000; hemoglobin, 85 per cent; white blood cells, 11,500 (neutrophils, 66, lymphocytes, 26, monocytes, 7, eosinophils, 1); nonprotein nitrogen, 48 mg., chlorides, 495 mg. per cent; and CO₂ combining power, 45 volumes per cent. The urine contained 100 mg. per cent of albumin. The spinal fluid was within normal range.

Death occurred at 9:05 P.M. on July 24, approximately 34 hours after the initial attack.

II. Acute Onset of Early Coma or Delirium, with Subsequent Partial Remission, a Prolonged Course, and Terminal Relapse

AIP Acc. 118078. An obese white male aged 25, was admitted to a hospital in Florida on September 6, 1944. While on a march that day he had suddenly collapsed and become unconscious. On admission he was in deep coma; the skin was hot and dry, the rectal temperature 110°F., the pulse 140 and of poor quality, the respiration 40 and stertorous, and the blood pressure 80/40 mm. Hg. Rhonchi were heard throughout the chest. There was pupillary constriction, and the tendon reflexes could not be elicited. Shortly after admission several generalized convulsions occurred.

During the first day of the illness the patient frequently vomited bloody fluid and was incontinent of urine and feces; the coma lifted slightly, the pupils began to react and the tendon reflexes reappeared. However, it soon was evident that there was rigidity of the neck, mild opisthotonos, and spasticity of the right arm and leg. On the second day the patient was restless, nuchal rigidity persisted, the eyes

deviated upward and to the left, and the head was held tilted to the left. Cutaneous petechiae were observed. On the fourth day coma persisted; there were râles in the chest. The temperature during the previous three days had fluctuated between 101 and 104°F. Treatment consisted of sponging, plasma transfusions, intravenous fluids, oxygen, cardiac stimulants, and sulfonamides. On the fifth day the patient's condition seemed to improve, but on the sixth his temperature rose to 108°F., the pulse to 160 and respirations to 60. From the eighth to the eleventh day the patient rallied and the temperature fell to 101°F. At this time he was mentally confused and unable to comprehend or speak. The blood pressure gradually rose to 130/78 mm. Hg. Oliguria became more pronounced. Electrocardiograms, initially abnormal, now were normal.

Examinations of the blood revealed the following: red blood cells, 4,050,000 to 5,210,000; hemoglobin, 76 to 102 per cent; white blood cells, 5,300 (neutrophils, 51, lymphocytes, 49) to 23,250 (neutrophils, 90, lymphocytes, 10); hematocrit, 36 to 58 per cent; chlorides, 412 to 449 mg. per cent; CO₂ combining power, 38 volumes per cent; total serum protein, 6.54 per cent (alb. glob. ratio: 4.4:2.14); and icterus index, 15 to 16. (The platelet count and the prothrombin and bleeding times are given in Table XII; the clotting time varied from 3½ to 4½ minutes.) The urine contained 2+ albumin and occasional casts and pus cells. The spinal fluid was within normal limits.

On the twelfth day the temperature rose to 103°F., bronchopneumonia became evident, and the patient lapsed into coma and died.

AIP Acc. 120161. A white male, aged 18, was admitted to a hospital in Texas on July 28, 1944. The day before he had complained of abdominal distress and of feeling hot, faint, and mentally confused. On admission he was delirious, being restless, resistive, apprehensive, suspicious, and disoriented. The skin was hot, dry and moderately cyanotic; the rectal temperature was 108°F., pulse 116, respirations 50, blood pressure 100/60 mm. Hg. (Fig. 2).

There were stiffness and cramping of leg muscles and hyperextension of the fingers. Extrasystoles and a soft apical systolic murmur were heard, but the electrocardiogram was normal. Therapy consisted of cold water sprays, massage, oxygen, intravenous 5 per cent glucose in saline, and vitamins C and B₁.

By the second day the temperature had fallen to 101°F. and the blood pressure had increased to 120/70 mm. Hg., but the delirium and cardiac irregularity persisted. The patient began to pass dark urine which showed a specific gravity of 1.013, was acid, and contained blood and 3+ albumin. Blood studies revealed the following: red blood cells, 4,500,000; hemoglobin, 105 per cent; white blood cells, 10,250 (neutrophils, 75, lymphocytes, 24); hematocrit, 46 per cent; and urea nitrogen, 25.9 mg. per cent. Following a transfusion of 500 cc. of plasma the temperature rose to 108°F. On the third day the temperature was again reduced by cooling measures and there was a slight improvement in the mental condition. On the sixth day there was twitching of the fingers, which was regarded as a manifestation of uremia.

From the third to the eleventh day of illness the patient showed progressive oliguria and azotemia. The nonprotein nitrogen increased from 133 to 231 mg., the urea nitrogen from 26.7 to 37.5 mg., creatinine from 5.5 to 10.6 mg., and uric acid from 5.9 to 6.1 mg. per cent. During the course of the illness the blood chlorides varied from 561 to 396 mg. per cent, the CO₂ combining power from 60.6 to 35.6 volumes per cent, and the blood leukocytes from 10,250 to 14,350. The blood pressure gradually rose to 180/110 mm. Hg. (Fig. 2).

The patient became more and more evidently uremic and died on August 8, approximately 11 days after the onset.

III. *Insidious Onset, Slowly Progressive Course, and Late Development of Coma*

AIP Acc. 102705. A white male, aged 22, was admitted to a hospital in Texas on August 14, 1943. For 4 days previously there had

been increasing weakness, nausea and vomiting, and tachycardia. Examination revealed dryness of the skin and tongue; the temperature was 99.4°F., pulse 128, respiration 24 and blood pressure 100/70 mm. Hg. (Fig. 1A). The patient appeared somewhat lethargic. He was placed on a "heat exhaustion regime." Blood studies revealed the following: red blood cells, 5,350,000; hemo-

The blood pressure was unobtainable, and the skin was cold, clammy, and cyanotic. The patient received a transfusion of 500 cc. of plasma and 1000 cc. of saline solution intravenously. Signs of circulatory failure became progressively more marked, death occurring on August 16. The entire illness lasted 6 days, but hyperthermia was present for only 18 hours.

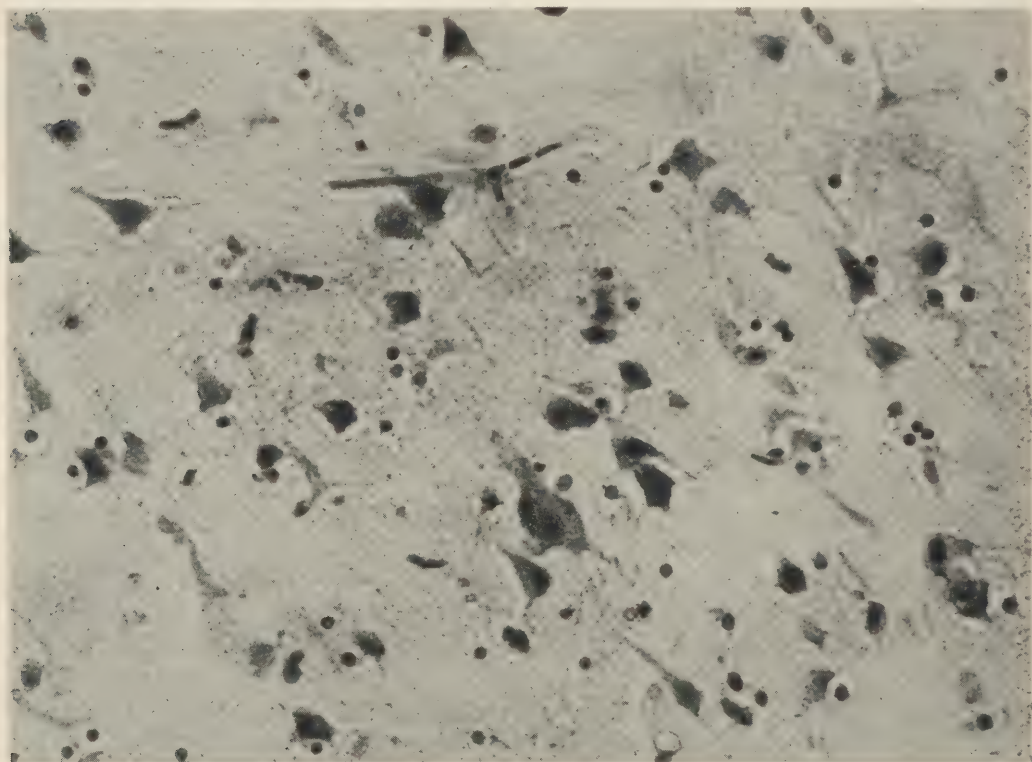


FIG. 4. Duration of illness, 11 hours. The cerebral cortex shows edema, congestion and severe cell disintegration. Cresyl violet stain. $\times 450$. AIP Acc. 114682.

globin, 85 per cent; white blood cells, 17,350 (neutrophils, 75, lymphocytes, 17, monocytes, 8); and urea nitrogen, 35.7 mg. per cent. The urine had a specific gravity of 1.019, and contained 2+ albumin, a moderate number of red blood cells and a few granular casts. The spinal fluid was slightly blood-tinged. On the second day following admission the patient became comatose; the temperature, after falling to 97.6°F., gradually rose to 106°F., the pulse became rapid and virtually imperceptible, and the respirations rapid and shallow.

PATHOLOGIC FINDINGS

The literature on the pathologic anatomy of heat stroke is relatively meager. It is agreed that changes occur both in the central nervous system and in the viscera, but most authors have regarded these changes as neither striking nor specific.

Central Nervous System

In approximately one-third of the 125 cases the entire brain was available for study. Information in regard to the others was obtained

from the protocols. In the great majority of cases the autopsies were performed within 15 hours of death, often in an hour or two; therefore post-mortem autolysis was minor or nonexistent.

The weight of the brain was usually increased, often by several hundred grams, and the average was 1493 gm. Most cases presented distinct edema of the leptomeninges

well defined, the blood vessels thin-walled and the ventricles of normal size.

PARENCHYMAL CHANGES. Examination of analogous areas of the brain in representative cases of varying duration revealed parenchymal changes which were either slowly or rapidly progressive.

Cerebral Cortex. Edema and congestion, as well as degenerative changes in the neurons

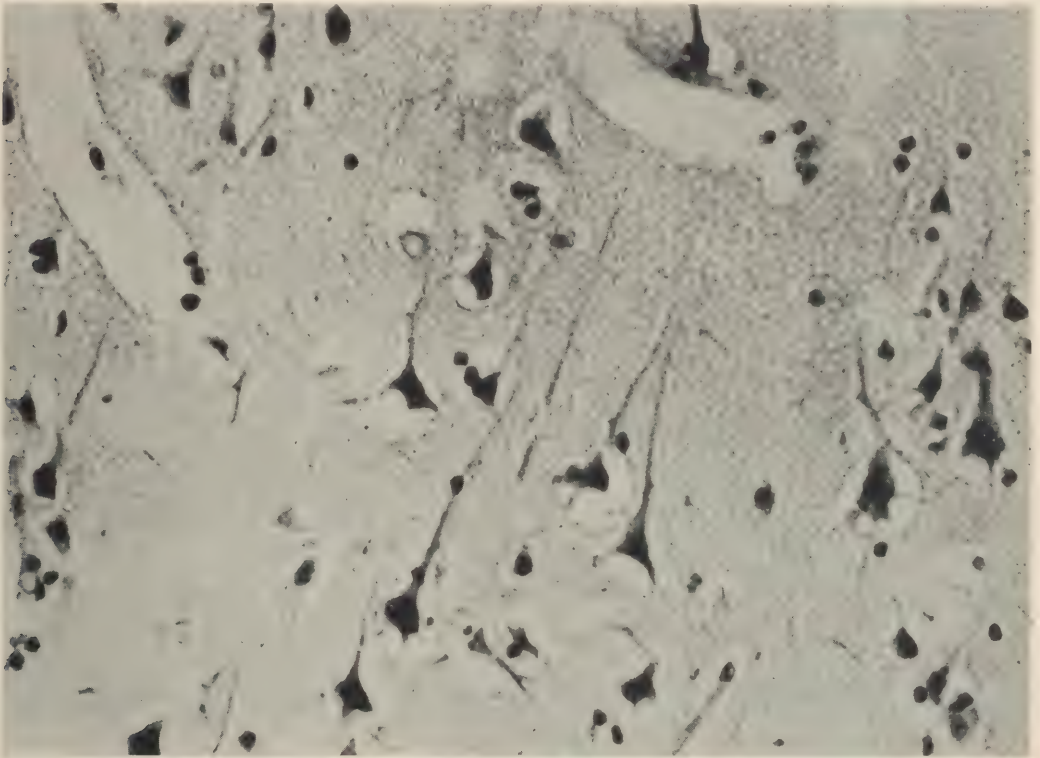


FIG. 5. Duration of illness, 72 hours, with 18 hours of hyperthermia. The cells of the cerebral cortex are considerably shrunken and hyperchromatic. The changes do not exceed those of the usual 18-hour case of heat stroke. Cresyl violet stain. $\times 450$. AIP Acc. 101118.

and the brain, a flattening of convolutions, and a cerebellar pressure cone. In approximately half of the cases the leptomeninges were diffusely congested, but the underlying brain showed only a patchy congestion, especially intense in the white matter and in the vicinity of the ventricles. No massive hemorrhages were observed; petechiae, however, were common in the walls of the third ventricle and the floor of the fourth ventricle, but were scant in the leptomeninges. There was no other gross change, the gray and white matter being

(Fig. 4) were found in a section of the frontal cortex from a representative case of 11 hours' duration. Most of the nerve cells and their dendrites were swollen, their cytoplasm chromatolytic or the seat of vacuolar disintegration, and their nuclei pyknotic. Some of the nerve cells had been transformed into "ghosts." At this stage there was no apparent reaction on the part of the glia. A somewhat later change is illustrated in a case of 18 hours' duration: the neurons were shrunken, had wire-like dendrites and hyperchromatic cyto-

plasm and nuclei (Fig. 5). Pericellular edema was evident, but glial reaction had not yet appeared. In cases of more than 24 hours' duration, the number of neurons was distinctly reduced and glia were beginning to proliferate. These changes were more pronounced the longer the illness. The most severe damage was seen in a case in which survival was 12 days (Fig. 6 and 7). The cyto-architectural

moderate increase in glial elements; no distinct demyelination was found, but fat stains revealed a slight increase of lipoids in nerve cells and occasional fat-laden gitter cells in perivascular spaces.

Basal Ganglia. The corpus striatum and thalamus had undergone changes less severe but similar to those in the cortex. In cases of brief duration, the nerve cells, particularly

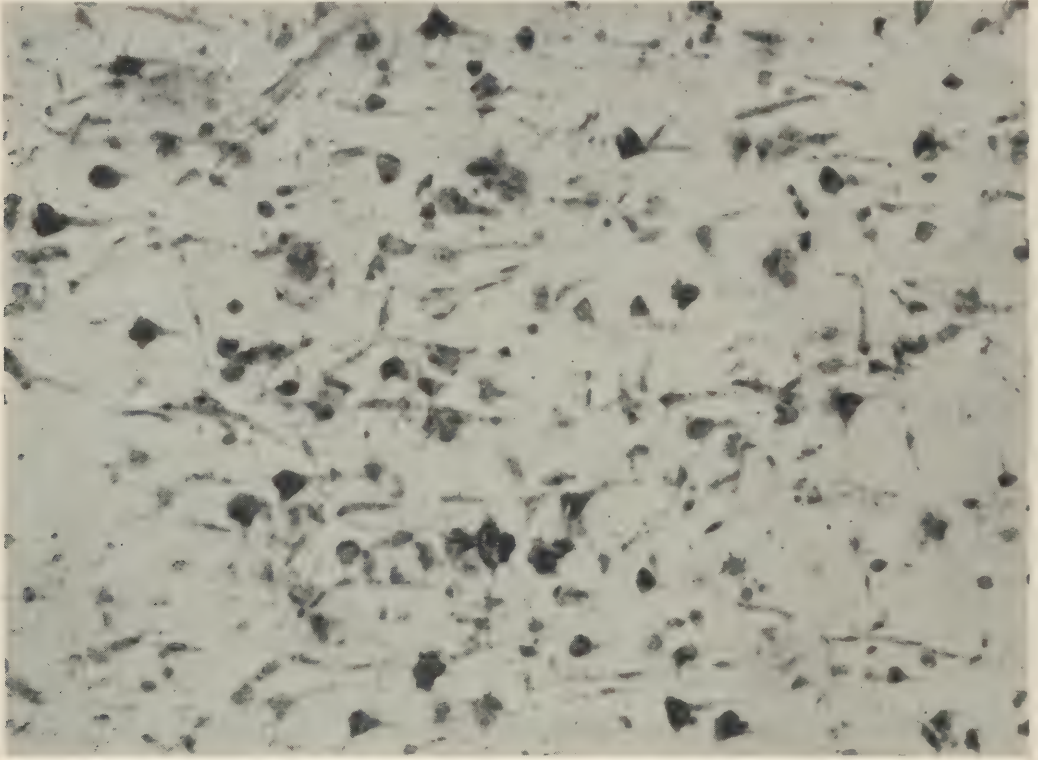


FIG. 6. Duration of illness, 276 hours. The cyto-architectural pattern of the cerebral cortex is considerably altered because of dropping out and degeneration of neurons and diffuse proliferation of microglia. Cresyl violet stain. $\times 300$. AIP Acc. 118078.

pattern was profoundly altered because of the disappearance of numerous nerve cells and the disintegration or hyperchromatosis of many of those that remained; there was also an extensive and diffuse proliferation of glia. Most of these cells were microglia, belonging mainly to the category of "rod" cells, but an increase of macroglia was also observed. The upper layers of the cortex were generally more affected than the lower. The white matter was relatively spared, there being only a

the large ones of the caudate nucleus and putamen, were diffusely damaged. In cases of longer standing a proliferation of glial elements had also taken place: microglia focally, especially around degenerating neurons, and macroglia diffusely. In the thalamus were focal collections of glia, most numerous in intercalated areas between the chief nuclei (Fig. 8). The globus pallidus was the least affected of the basal ganglia. No glial proliferation was noted in the periventricular system.

Cerebellum. Changes in the cerebellum were more striking, more consistent, and more rapid in development than in any other part of the brain. When death occurred in less than 24 hours, edema of the Purkinje layer was marked and the number of Purkinje cells was reduced, those remaining being swollen, pyknotic, or disintegrated. The molecular and granular layers, on the other hand, were not

layer, where only the remnants of Purkinje cells remained, but there was only moderate increase in the microglial cells of the molecular layer (Fig. 11). In another case of 3 days' standing, glial elements had proliferated to about equal degree in the Bergmann and molecular layers (Fig. 12), and under high magnification the few remaining Purkinje cells were found to be in a state of coagulation ne-

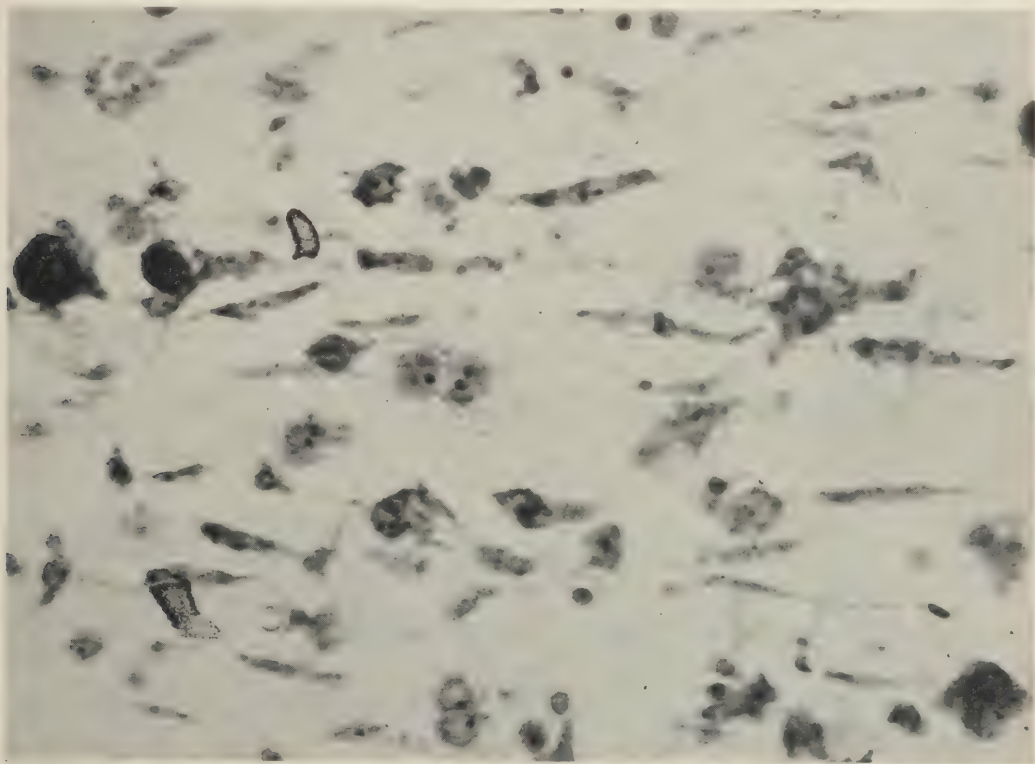


FIG. 7. Duration of illness, 276 hours. This is another field from the case illustrated in Figure 6, showing the proliferation of microglia and of some astrocytes in greater detail. Cresyl violet stain. $\times 600$. AIP Acc. 118078.

altered except for a moderate proliferation of satellite oligodendroglia (Fig. 9 and 10). When survival was more than 24 hours there was almost complete degeneration of the Purkinje layer and gliosis of corresponding severity. The glial reaction was first evident in the Bergmann layer, and soon afterward in the molecular layer. By the end of 3 days, one or the other or both of these alterations were pronounced. Thus, in one case of 3 days' duration a marked proliferation of the astrocyte-like forms was noted in the Bergmann

crisis. The most advanced changes were noted in a case of 12 days' duration: the molecular and Bergmann layers were hyperplastic, the granular layer rarefied (Fig. 13), and remaining Purkinje cells all but consumed by macrophages (Fig. 14). The changes in the cerebellum were equally pronounced in hemispheres and vermis. The dentate nucleus was similarly affected. In a case with a survival period of 11 hours most of the neurons of the dentate nucleus were hyperchromatic and beginning to disintegrate (Fig. 15). Damage to



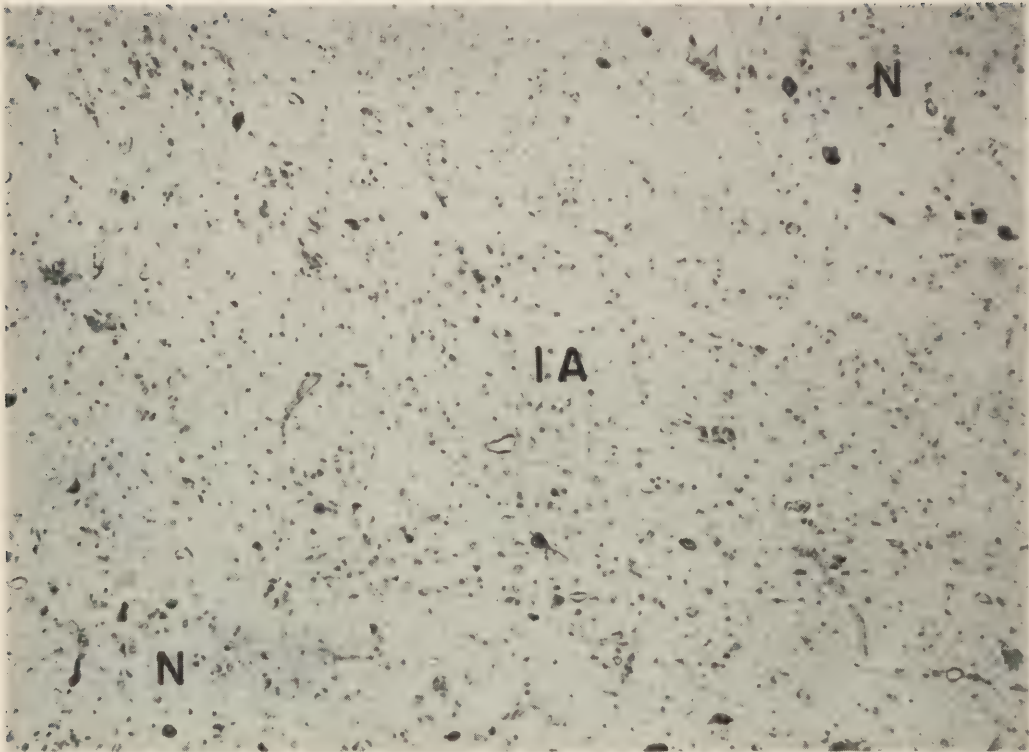


FIG. 8

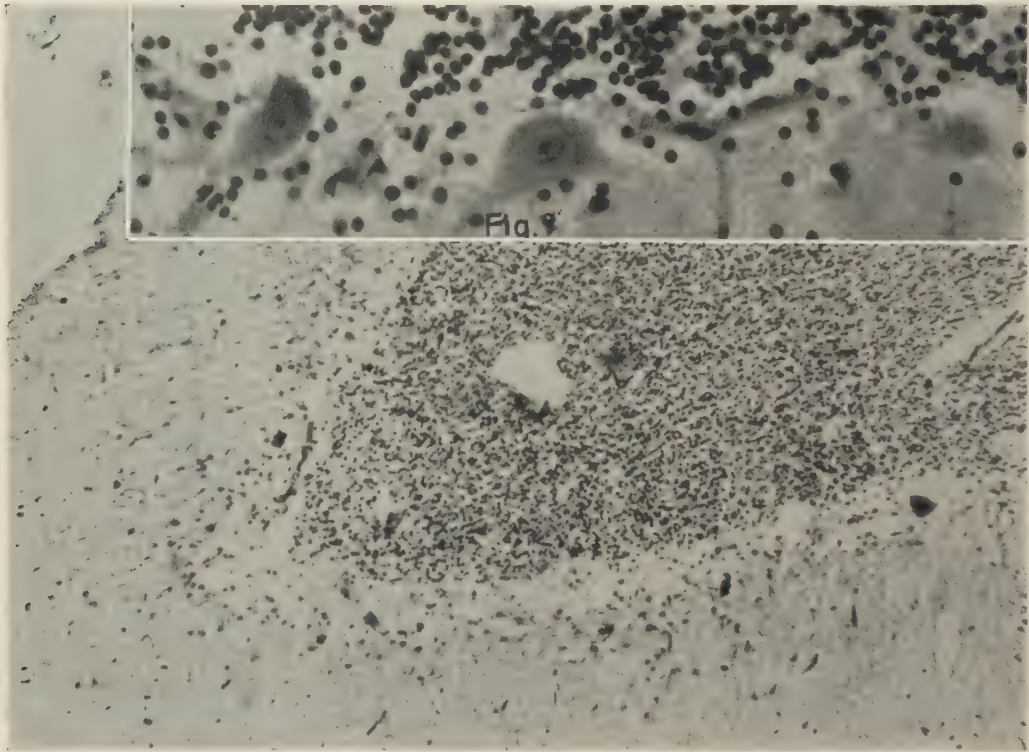


FIG. 10

this nucleus was so great in a case of 12 days' standing that it could hardly be identified since most of the neurons had been replaced by glia (Fig. 16). High magnification of gliotic regions revealed a predominance of microglia over macroglia and abundant neuronophagia.

Hypothalamus. The hypothalamus was carefully investigated in view of its well recognized role in the regulation of body temperature. Like other portions of the brain, the hypothalamic nuclei were subject to edema during the early stages of the disorder. Later, however, no significant alteration was observed. Occasionally slight general depopulation of neurons and a mild increase in glial cells seemed apparent but the changes were so equivocal that they could not be regarded as significant. The hypothalamus in cases of different duration is illustrated in Figures 17 to 20 inclusive. The lack of demonstrable damage here contrasts with the condition in other portions of the brain.

Midbrain, Pons, Medulla Oblongata and Spinal Cord. Nerve cells and glia were generally normal in number and appearance. Mild damage of nerve cells and slight gliosis were observed only in the quadrigeminal region, the inferior olivary nuclei, and the reticular formation.

HEMORRHAGES. Hemorrhages were present in the brain in 65, and in the leptomeninges in 20 of the cases (Table XV). The cerebral hemorrhages usually were confined to perivascular spaces and were not conspicuous. Leptomeningeal hemorrhages, on the other hand, tended to be diffuse (Fig. 21) and were generally most severe in cases of brief duration. Regardless of the length of illness, the red blood cells in the hemorrhagic areas were intact, suggesting that the seepage was relatively recent.

Although hemorrhages varied in location from case to case they were most pronounced in the walls of the rostral part of the third ventricle. Thus, they were found in the periventricular system (Fig. 17), the paraventricular nucleus (Fig. 22), the supraoptic nucleus (Fig. 23), the more medial parts of the ventromedial and dorsomedial hypothalamic nuclei, somewhat less often in the perifornical and septal regions and the medial portion of the thalamus. The caudal part of the hypothalamus was less affected, the hemorrhages being mainly in the posterior hypothalamic nucleus and the adjacent periventricular system. No hemorrhages were observed in the mamillary body. In the midbrain, the periaqueductal region and the oculomotor nuclei were the sites of predilection (Fig. 24). Hemorrhages of the pons and medulla oblongata were restricted to the floor of the fourth ventricle, most frequently in and near the dorsal efferent nucleus of the vagus (Fig. 25).

Hemorrhages were encountered occasionally in the cerebral cortex, white matter, striatum, pallidum, nucleus basalis, subthalamus, cerebellum, and the tegmental and ventral portions of the lower brain stem. In two cases, unique in our series, the cerebral white matter was extensively affected, with widespread and well developed "brain purpura" in one (Fig. 26), and countless perivascular foci of rarefaction in the other (Fig. 27).

DISCUSSION OF THE PATHOLOGIC CHANGES IN THE BRAIN. The authors of reports on some of the large series of heat stroke, McKenzie and Le Count³⁵ and others, emphasize the frequency with which cerebral edema and congestion occur. Hemorrhages also have been commonly noted. In certain

FIG. 8. Duration of illness, 276 hours. The thalamus displays a reduction in neurons and proliferation of glia, especially in intercalated areas (IA) between chief nuclei (N). Cresyl violet stain. $\times 144$. AIP Acc. 118078.

FIG. 9. Duration of illness, 5 hours. The Purkinje cells of the cerebellum are swollen and disintegrated, and are surrounded by oligodendroglial satellites. Cresyl violet stain. $\times 450$. AIP Acc. 85367.

FIG. 10. Duration of illness, 5½ hours. In the cerebellum there is 'dropping out' and disintegration of Purkinje cells as well as edema of the Bergmann layer. $\times 135$. AIP Acc. 99088.

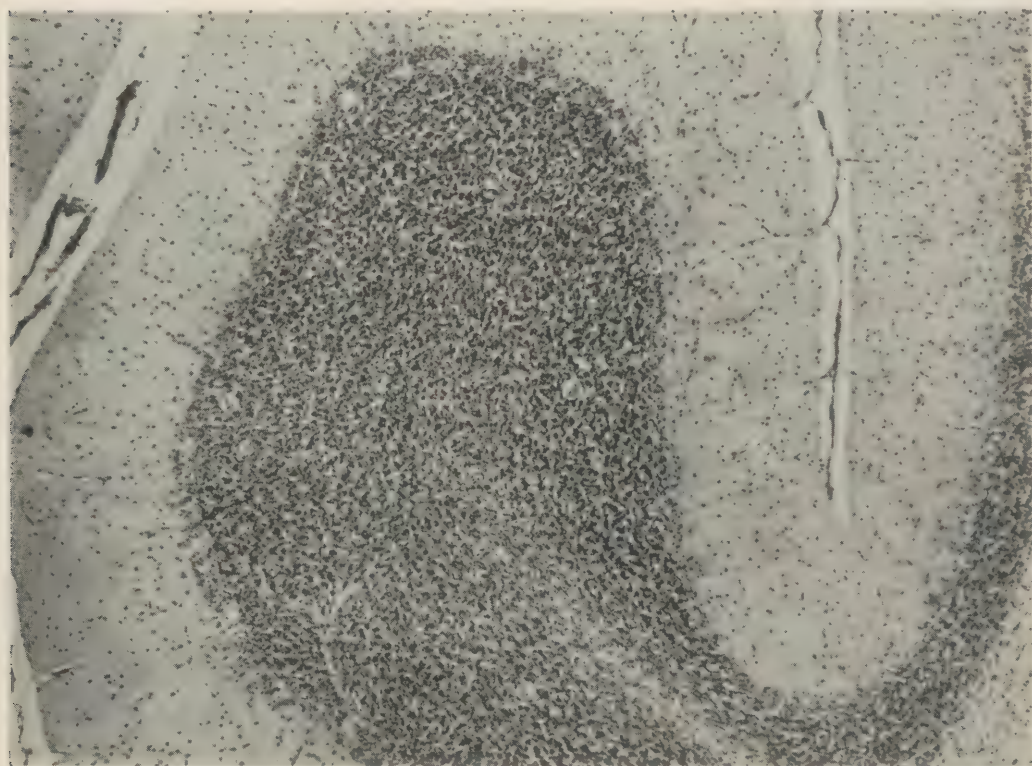
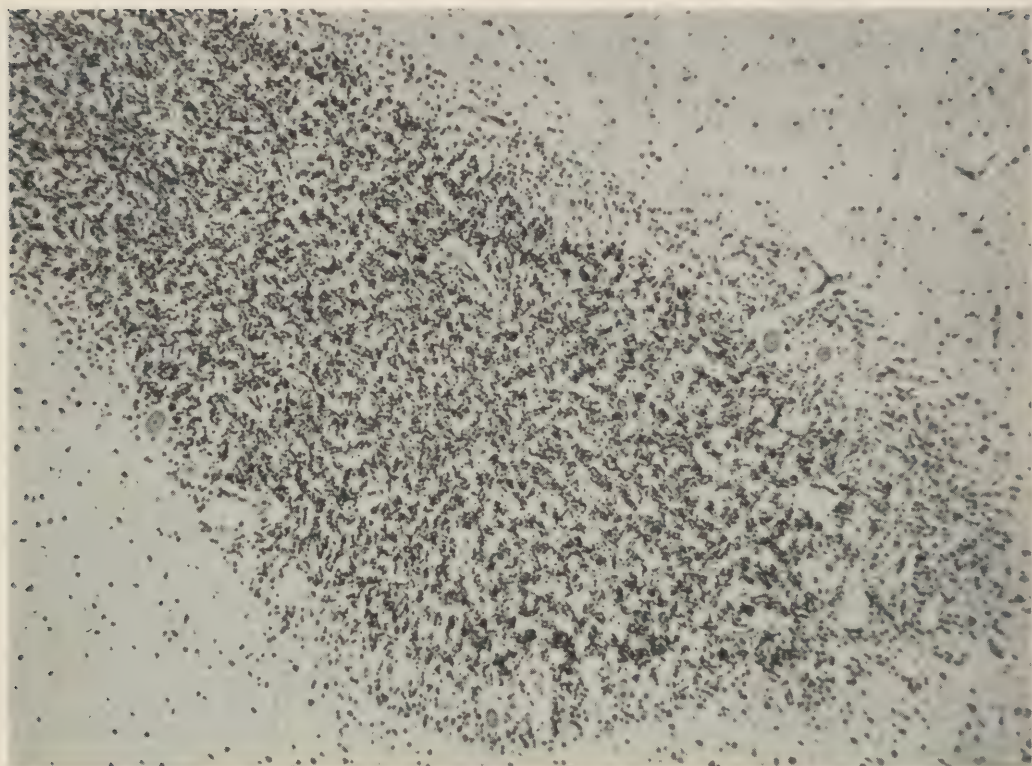


FIG. 11. Duration of illness, 72 hours. The Purkinje cells of the cerebellum have almost completely disappeared and there is proliferation of glia in the Bergmann layer. Cresyl violet stain. $\times 130$. AIP Acc. 96554.

FIG. 12. Duration of illness, 72 hours. The glial cells of the molecular and Bergmann layers of the cerebellum are hyperplastic and the Purkinje cells have largely disappeared. Cresyl violet stain. $\times 65$. AIP Acc. 101158.

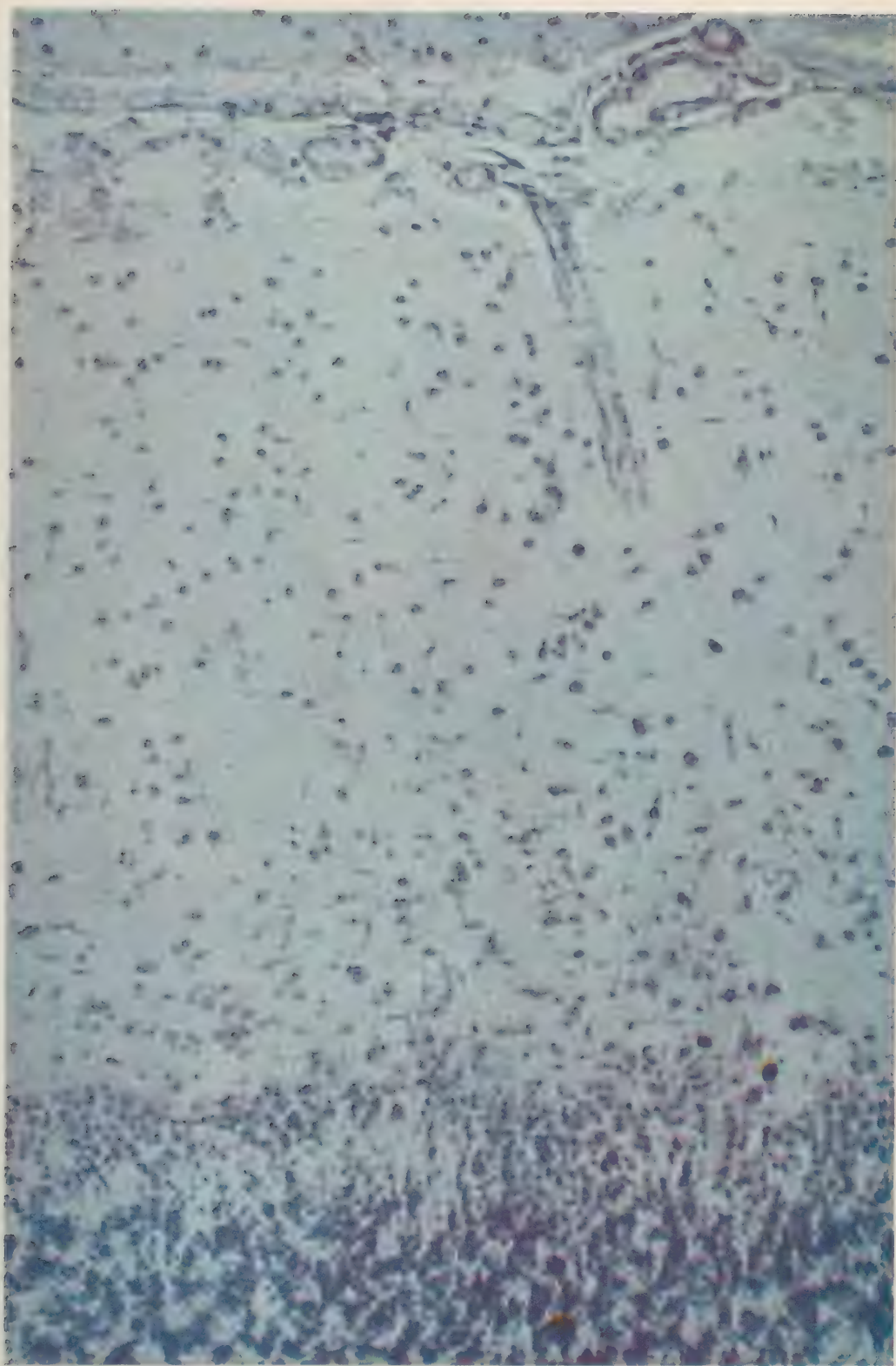


FIGURE 13. Duration of illness, 276 hours. There is marked proliferation of glia in the molecular layer, disappearance of Purkinje cells, and rarefaction of the granular layer. Cresyl violet stain. X90, AIP Acc. 116078.

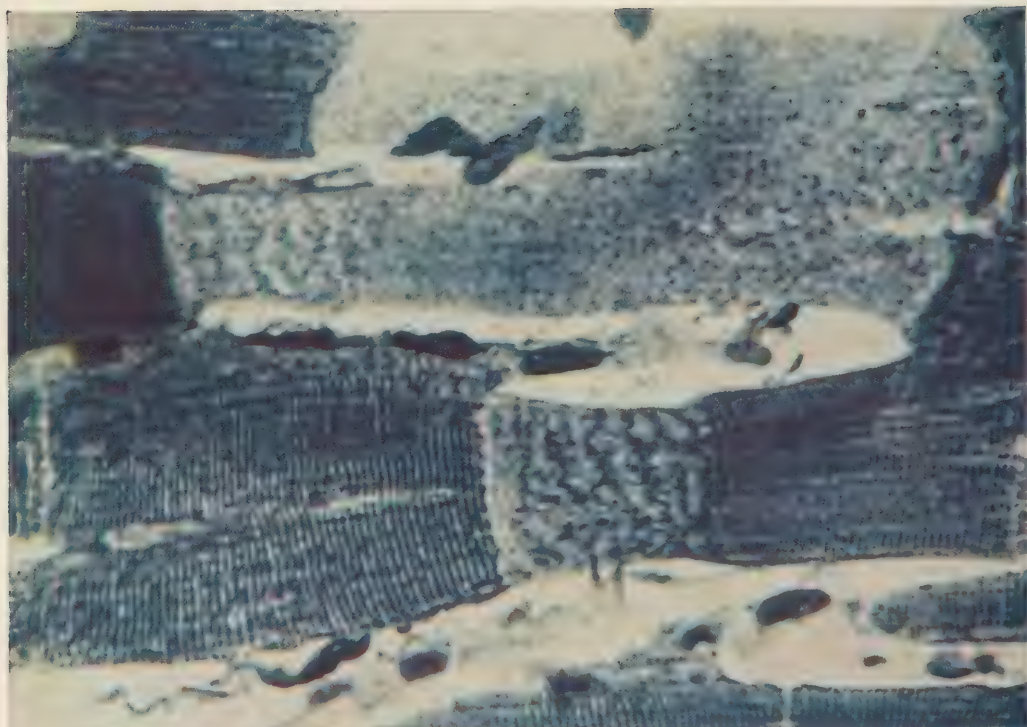


FIG.
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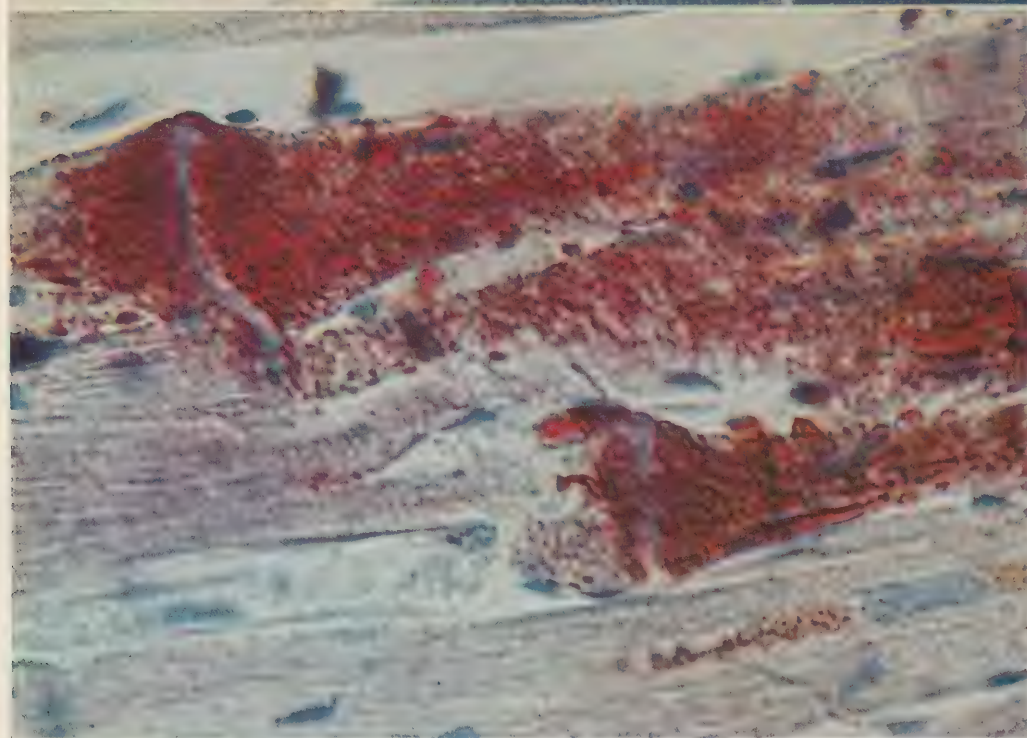


FIG.
37

FIGURE 36. Duration of illness, 96 hours. The photograph illustrates that breakdown of intrinsic muscle structure may begin in the portion of a segment adjacent to an intercalated disk. Some of the segments of muscle fibers are completely amorphous. Bodian stain. AIP Acc. 95093.

FIGURE 37. Duration of illness, 10 hours. Considerable fat is present in degenerated muscle segments. Sudan III. AIP Acc. 99987.

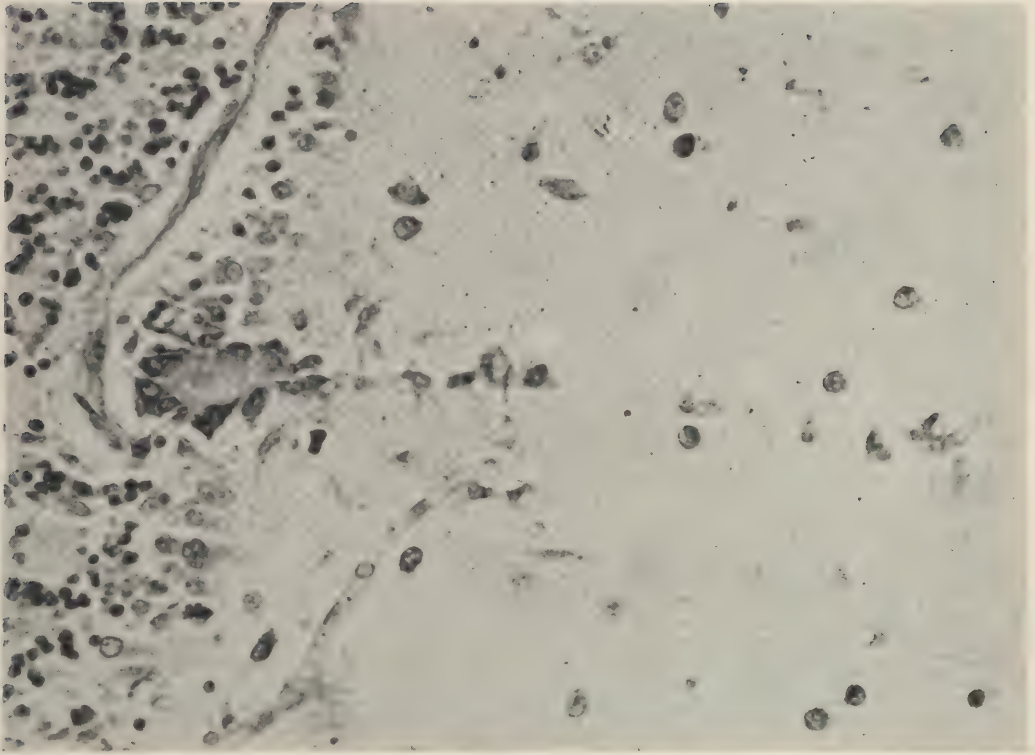


FIG. 14. Duration of illness, 276 hours. A degenerated Purkinje cell and its apical dendrite are in the process of phagocytosis by glial elements. Cresyl violet stain. $\times 450$. AIP Acc. 118078.

cases, hemorrhage constituted the most conspicuous finding: for instance, severe "brain purpura" was described by Schwab,⁴⁹ hemorrhage into the putamen by Schwartz,⁵⁰ and widespread hemorrhages into the leptomeninges by Fleck and Hückel.¹⁷ Encephalomalacia (Stern,⁵³ M'Kendrick³⁴), perivascular rarefaction (Rosenblath⁴⁷), and presumed internal capsular hemorrhage associated with hemiplegia (Messiter³⁶) also have been observed but are exceedingly rare.

Degeneration of nerve cells, either in the form of acute swelling or shrinkage and pyknosis, has been regarded as a significant finding by some authors (Hartman and Major²⁴), but others have believed it to be a post-mortem artifact. Omorokow⁴¹ has expressed the opinion that high temperature causes necrosis by inducing coagulation of neuroglobulin.

In our opinion the cellular changes in the brain are essentially the result of hyperthermia whereas the hemorrhages, congestion, and

edema are chiefly secondary phenomena coincident with shock; hemorrhage is probably exaggerated by a clotting defect resulting from the thrombocytopenia already mentioned. Degenerative neuronal change was a constant feature in all our cases of heat stroke, and could be traced through successive stages from acute and chronic cell alteration to disappearance of neurons and their replacement by glia. Moreover, it was observed that the changes corresponded to the length of survival after the onset of hyperthermia, not to the duration of the illness in the event that the hyperthermia was only terminal. Thus, in a case of "heat exhaustion" of 72 hours' duration (Case 101118), in which hyperthermia developed in the last 18 hours of life, there was considerable damage to neurons but neither cellular disintegration nor glial proliferation (Fig. 5). We regard the irreversible damage to the central nervous system as seen in our cases as adequate pathologic basis for the cerebellar and mental sequelae which have been re-

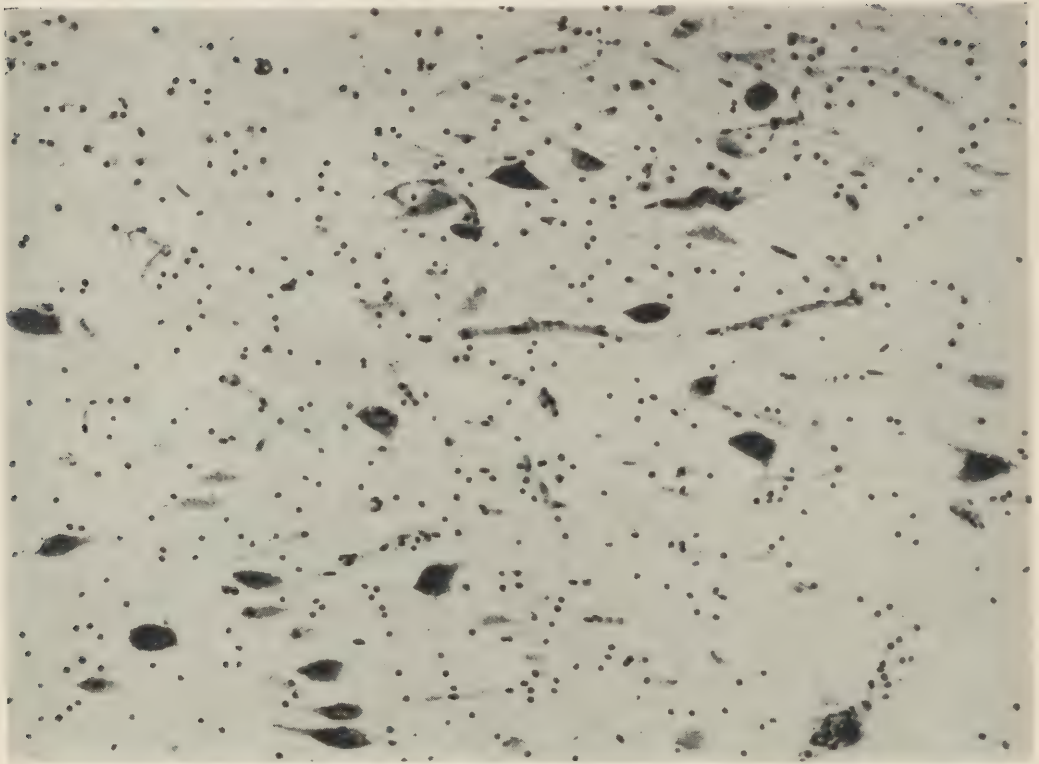


FIG. 15

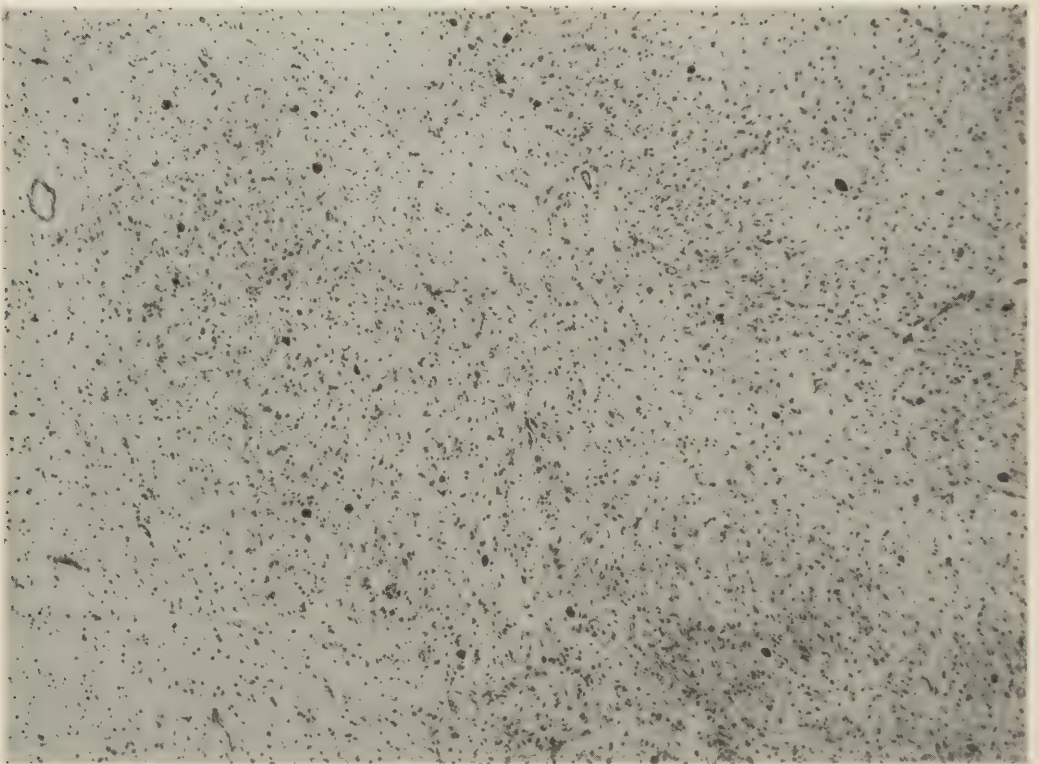


FIG. 16

ported in nonfatal heat stroke (Antheaume and Mignot,⁴ Freeman and Dumoff,¹⁸ Goebel,²² Shepherd,⁵¹ Stewart,⁵⁴ Wakefield and Hall,⁵⁸ Weisenburg⁶³).

Edema, congestion, and hemorrhage were inconstant and were not related to the degree of hyperthermia. A direct relationship existed, however, between the severity of hemorrhage

the same as in numerous other disorders terminating in shock but not associated with hyperthermia.

It is recognized that a relative anoxia exists in shock (Kopp and Solomon³⁰) and that the oxygen partial pressure of arterial blood may fall as much as 25 per cent (a reduction comparable to that resulting from an ascent to an

TABLE XIV

A CORRELATION OF BLOOD PRESSURE READINGS (AS INDEX TO THE SEVERITY OF SHOCK) WITH THE DEGREE OF CEREBRAL HEMORRHAGE IN 12 CASES OF HEAT STROKE

AIP Acc.	Duration of Illness (Hrs.)	Adm. Temp. (° F.)	Blood Pressures	Pulse Pressures	Degree of Cerebral Hemorrhage		Chief Sites of Hemorrhage
					Severe to Mod.	Mild	
120160	3	110°	70/0, 60/0, 90/50	70, 60, 40	+		Septal, perifornical & ant. periventricular regions, paraventricular nucleus, & floor of IVth ventricle.
112744	4	111°	80/55	25	+		Ant. periventricular & medial hypothalamic regions.
99612	8	109°	60/0, 110/60	60, 50	+		Ant. periventricular & suprachiasmatic regions.
118077	12	110°	100/60, 120/80, 108/56, 70/50	40, 40, 52, 20	+		Septal, preoptic & subcommissural regions, & paraventricular nucleus.
99261	16	107°	84/50, 80/60	34, 20	+		Periventricular region (from ant. commissure to corpus Luysi).
120159	18	110°	80/0, 100/50, 140/80, 82/64, 80/60	80, 50, 60, 18, 20	+		Thalamus, medial hypothalamus (ant. part), paraventricular nucleus, & region of nucleus basalis.
115914	2½	108°	150/90	60		+	Ant. periventricular region.
117740	7	110°	120/90	30		+	Thalamus & septal region.
114682	11	109°	130/70, 100/60	60, 40		+	Floor of IVth ventricle & subcommissural & post. periventricular regions.
98176	19	109°	122/70	52		+	Periventricular region (lat. & IIIrd ventricle) & supraoptic nucleus.
115309	120	109°	142/30, 82/52, 96/60, 120/80	112, 30, 36, 40		+	Medial hypothalamus (ant. part).
120161	240	108°	100/60, 110/70, 114/66, 106/70, 120/80, 110/90	40, 40, 48, 36, 40, 20		+	Medial hypothalamus (ant. & post.).

and the degree of shock. Study of a number of cases picked at random indicated that when shock, as manifested by a lowering of blood pressure, was profound, the hemorrhages in the brain tended to be pronounced, but when the blood pressure was normal or slightly reduced they were usually minimal (Table XIV). Moreover, the site, distribution, and appearance of the hemorrhages were much

elevation of 17,500 feet) in therapeutic hyperthermia of 105°F., even though oxygen saturation of arterial blood and the arteriovenous oxygen difference are normal (Cullen, Weir and Cooke¹⁵). Although this degree of deficit in oxygen partial pressure may lead to apprehension and other mental symptoms, it is improbable that anoxia is a significant cause of changes in the brain in heat stroke. Con-

FIG. 15. Duration of illness, 11 hours. Neurons of the dentate nucleus are hyperchromatic, and there is moderate capillary engorgement. Cresyl violet stain. $\times 230$. AIP Acc. 114682.

FIG. 16. Duration of illness, 276 hours. The dentate nucleus has undergone extensive gliosis. Only a few shrunken neurons remain. Cresyl violet stain. $\times 75$. AIP Acc. 118078.

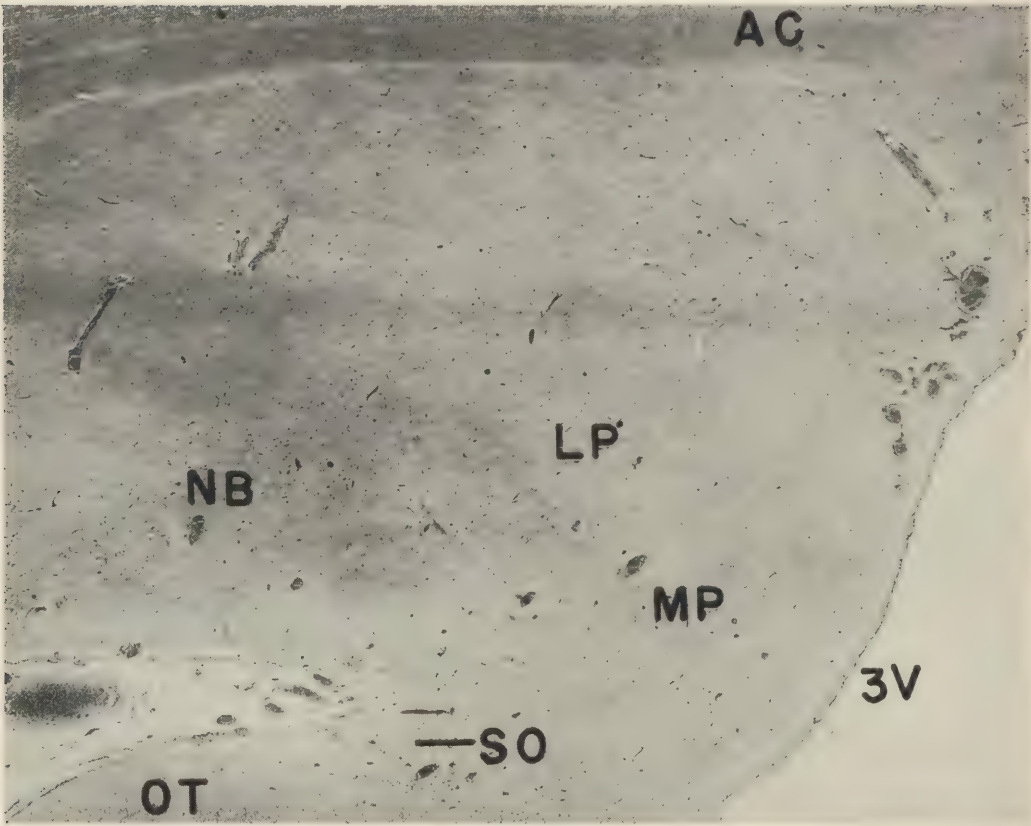


FIG. 17

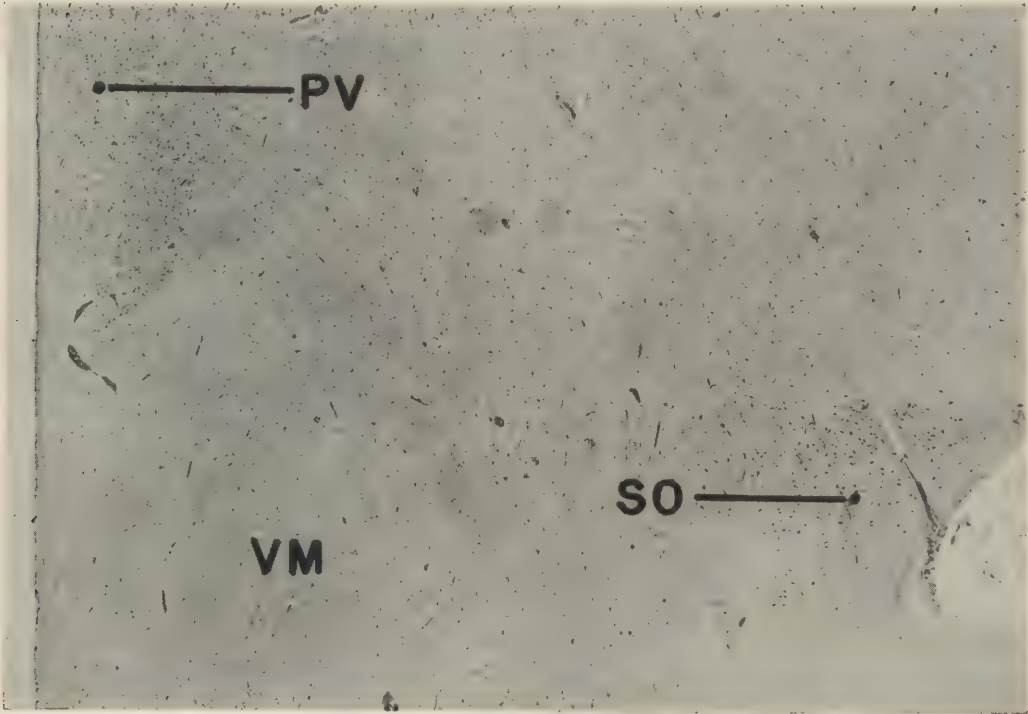


FIG. 18

siderably greater degrees of anoxia may have no deleterious effect. Ward and Olsen⁵¹ have related the case of an aviator who, owing to depletion of his oxygen supply, was without supplemental oxygen at altitudes between 25,000 and 20,000 feet for 39 minutes, and at altitudes between 20,000 and 12,000 feet for an additional 16 minutes; he was unconscious for 8 hours and semiconscious for 12 more hours and yet recovered completely. The lack of neurologic residua following deprivation of oxygen to the point of unconsciousness has been noted also by Horvath, Dill and Corwin,²⁶ and von Tavel.⁵⁵ On the other hand, Titrud and Haymaker⁵⁶ have reported profound mental changes in aviators subjected to sudden and severe anoxic insult: in one instance in which the patient was exposed to an atmosphere at 24,000 feet for 10 minutes there was complete mental incapacitation during the ensuing 3 weeks until death occurred as the result of massive hemorrhage from an esophageal ulcer; in another instance, in which the patient was deprived of supplemental oxygen during a forced descent from 27,000 to 7,000 feet, much the same clinical picture was observed for three weeks, after which the patient was lost sight of. Pathologically, the findings differed considerably from those observed in heat stroke: thus, in the case of anoxia of three weeks' standing, there was severe degeneration of the lower laminae of the cerebral cortex, massive necrosis of the striatum, focal necrosis of the globus pallidus, and relative sparing of the cerebellum; whereas in heat stroke the cerebral cortex was diffusely affected, the striatum and globus pallidus were almost untouched, and the cerebellum was seriously damaged. Lesser involvement of the central nervous system in anoxia has been reported by Gildea and Cobb²¹ and

van Bogaert *et al.*⁵⁷ The pathologic changes reported by Windle, Becker and Weil⁶⁸ in guinea pigs temporarily asphyxiated at birth also differed from those of heat stroke. In these animals a variable degree of neuronal necrosis in the central nervous system was observed, and there were swarms of microglia which had advanced from the subependymal cell plate of the fourth and lateral ventricles into adjacent structures, ultimately permeating most of the brain. In our cases of heat stroke no cellular activity was noted in the region of the ependyma, the microglia seeming to proliferate only in damaged areas.

The next question that may be raised is whether or not the hyperthermia in heat stroke may be an outcome of shock. It is well known that a moderate elevation of rectal temperature is the rule in the early phases of shock, whatever its cause, since the escape of body heat is prevented by peripheral vasoconstriction (Wright and Devine,⁶⁹ Blalock and Price⁹). The excessive subsequent rise may be accounted for 1) by a progressive accumulation of heat in the body owing to peripheral vasoconstriction and 2) a greater production of body heat brought about by increased metabolism. Kopp²⁹ and Kopp and Solomon³⁰ have found in fever therapy that for each degree of rise in body temperature there is an elevation of from 5 to 14 per cent in the metabolic rate, and that at levels of 106°F. and above the metabolic rate per degree of fever tends to increase even more sharply. Accelerated output of adrenalin doubtless contributes to this elevation in metabolism. It would seem logical to conclude that hyperthermia develops in shock because the central mechanism for heat dissipation is incapacitated and that instrumental in heat conservation is overactive, a view substantially the same as that held by Hyndman and

FIG. 17. Duration of illness, 4 hours. Admission T. 111°F.; B. P. 80/55. A transverse section of the brain at the level of the subcommissural and preoptic regions and the anterior portion of the optic tract (OT) discloses scattered petechial hemorrhages beneath the anterior commissure (AC) adjacent to the third ventricle (3V) and in the supraoptic nucleus (SO). The medial and lateral preoptic nuclei (MP and LP) and the nucleus basalis (NB) have a normal appearance. $\times 20$. AIP Acc. 112744.

FIG. 18. Duration of illness, 8 hours. Admission T. 109°F.; B. P. 132/70. The section is through the anterior portion of the hypothalamus, showing the paraventricular (PV), supraoptic (SO) and ventromedial (VM) nuclei. No significant changes are visible. Cresyl violet stain. $\times 20$. AIP Acc. 98175.

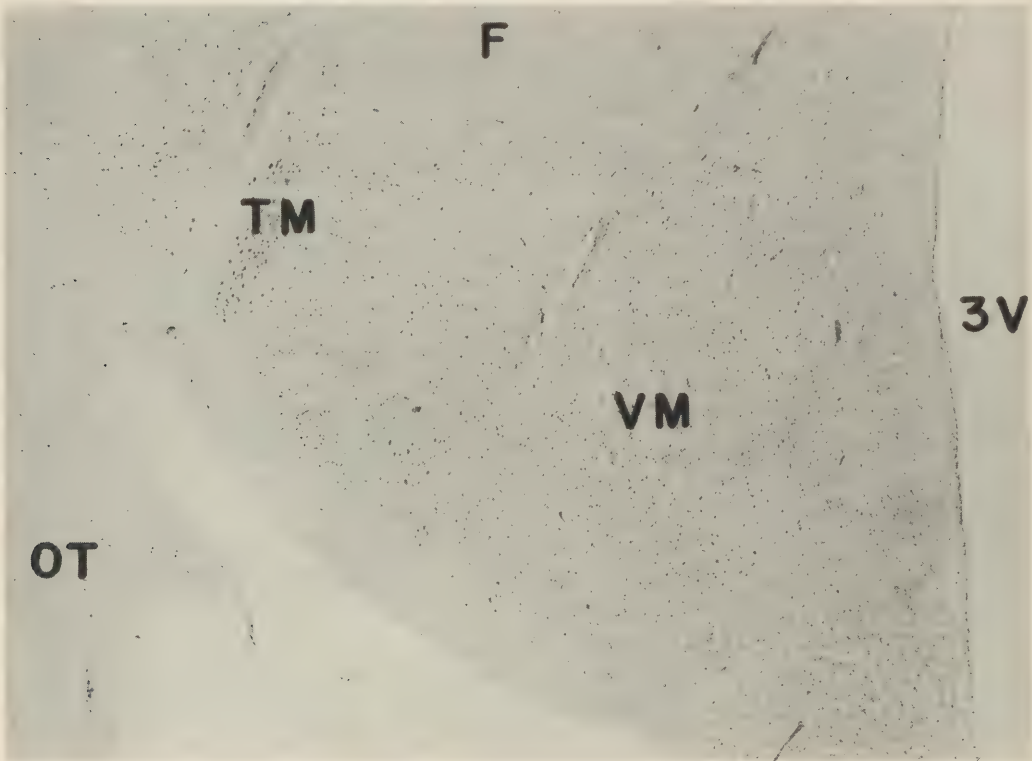


FIG. 19

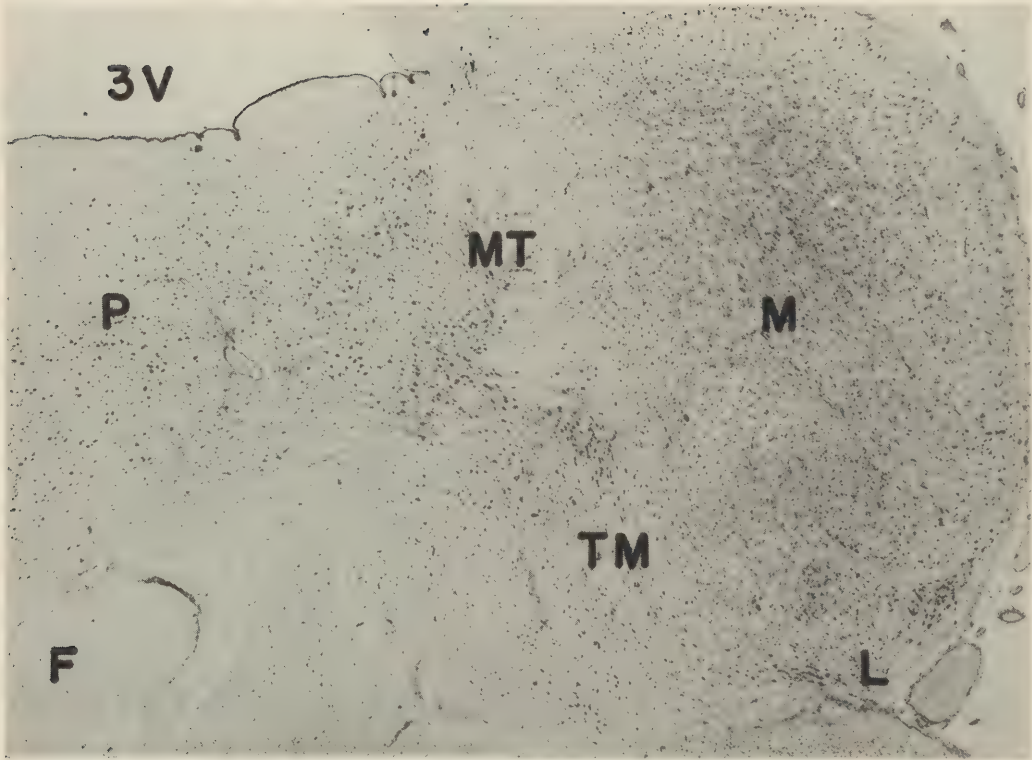


FIG. 20

Wolkin.²⁷ The same conclusions would apply to heat exhaustion terminating in hyperthermia, an example of which (Case 102705) is described under *Illustrative Cases*.

In attempting to frame a concept as to the cause of heat stroke one has to take into consideration not only the mechanism by which body heat is dissipated but also the conditions of the external environment. Body heat is lost entirely through physical means, but may be reduced by a lowering of basal metabolism. In an individual doing light muscular work at ordinary room temperature, radiation, convection, and conduction account for 70 per cent of heat loss, evaporation from the skin 14.5 per cent, vaporization of water from the lungs 8.0 per cent, the warming of inspired air 2.5 per cent, the loss of heat from the urine and feces 1.5 per cent, and by other means 3.5 per cent (Gemmill²⁰). In a warm atmosphere, the loss of body heat is accelerated in a number of ways, of which the most significant are sweating and a redistribution of blood so that a greater amount reaches the skin. It is apparent, however, that the temperature-regulating mechanism of the body is capable of adequate function only within certain limits of external environment. If the temperature of the air and of surrounding objects is higher than body temperature, the body will gain heat by radiation, convection, and conduction, leaving evaporation from the skin and vaporization of water from the lungs the only significant cooling mediums; thus, evaporation and vaporization, instead of accounting for the customary 22.5 per cent of heat loss from the body, now become responsible for nearly 100 per cent of heat loss. High vapor pressure (absolute humidity) will vitiate these last natural means of maintaining normal body tempera-

ture, whereupon the increase may reach such a point that the temperature-regulating mechanism is damaged and a vicious cycle established. In this connection it should be pointed out that despite impending collapse, the men whose histories are represented in our series often had expended every effort to continue their march or other activity, thus increasing further the body heat-load at a time when the capacity for heat dissipation was critically impaired by the high temperature and high vapor pressure of the external environment (Shickele⁴⁸). Taking these factors into consideration, the following sequence may be postulated: 1) the precipitating cause of heat stroke is excessive body heat; 2) the excess heat incapacitates the central heat-dissipating mechanism; 3) as a result sweating ceases, causing a greater accumulation of heat in the body; 4) with the rise of body temperature the increasing metabolism adds further fuel to the flames; 5) sooner or later shock usually ensues and, owing to peripheral vasoconstriction, further augments the body temperature. The shock may be brought under control, but the damage to the brain induced by the hyperthermia has been done. This hypothesis is at variance with that of Adolph and Fulton² who believed heat stroke to be the result of circulatory failure occasioned by the following series of events: 1) stimulation of the skin by heat, leading to reflex sweating and sometimes to a progressive deepening and acceleration of respiratory movements; 2) a resultant loss of carbon dioxide from the blood, particularly in the sweat; 3) a decrease in resistance of peripheral blood vessels, followed by a significant reduction in the volume of circulating blood, the heart compensating for the lack of venous return of the blood by beating

FIG. 19. Duration of illness, 130 hours. Admission T. 109°F.; B. P. 140/30, 95/60, 120/80. The section of the hypothalamus is at the level of the ventromedial (VM) and tuberomamillary (TM) nuclei. The fornix (F), optic tract (OT) and third ventricle (3V) are indicated. No changes are observed. Cresyl violet stain. $\times 20$. AIP Acc. 115309.

FIG. 20. Duration of illness, 14 hours. Admission T. 108°F.; B. P. not recorded. A transverse section of the hypothalamus at the level of the mamillary body shows a normal appearance of the medial (M) and lateral (L) mamillary, the tuberomamillary (TM) and the posterior hypothalamic (P) nuclei. The fornix (F), mamillothalamic tract (MT) and third ventricle (3V) are designated. Cresyl violet stain. $\times 20$. AIP Acc. 98163.

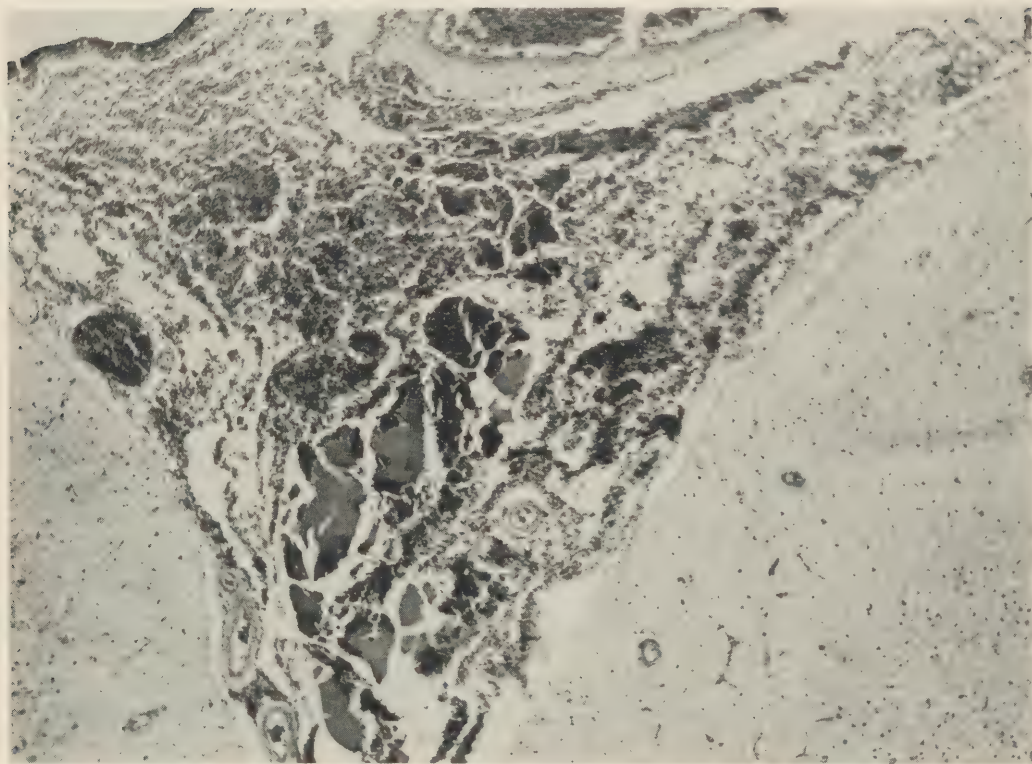


FIG. 21

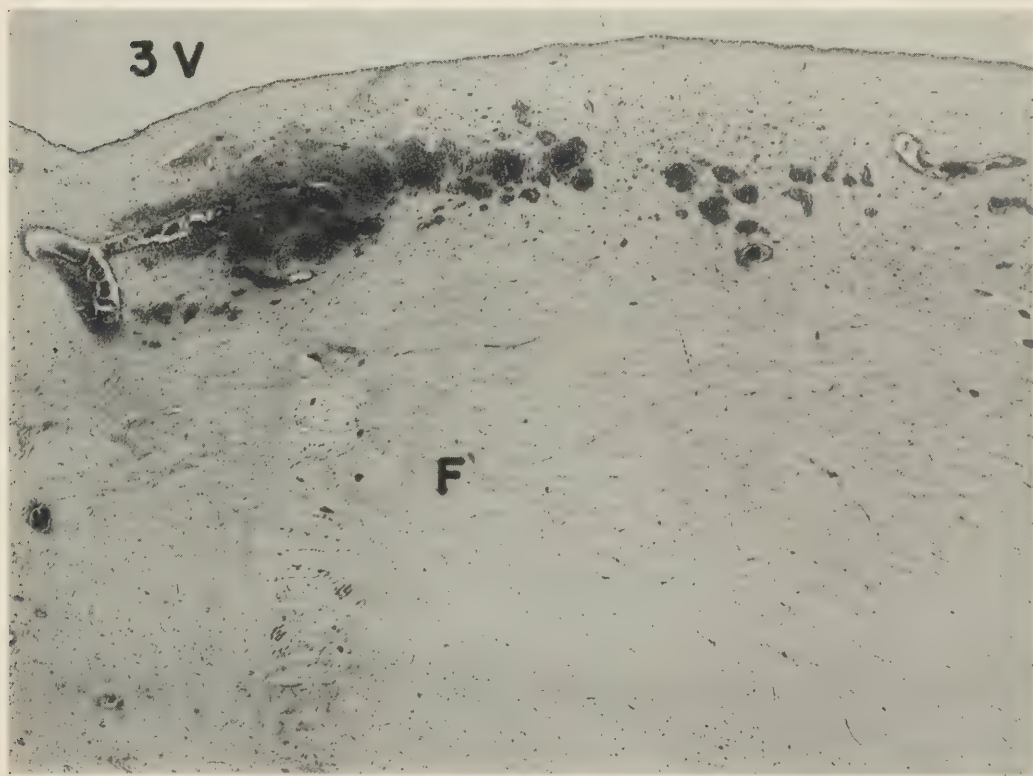


FIG. 22

faster, and leading ultimately to "a type of circulatory failure which would have to be included under the general category of shock." It is possible that the cases studied by Adolph and Fulton may fall into a different category than the great majority of our series, for theirs are apparently heat exhaustion complicated by shock and hyperthermia, while ours are instances of primary heat stroke.

Our attempt to demonstrate structural changes in the portions of the hypothalamus concerned with temperature regulation was unsuccessful. The work of Ranson and his associates,⁴² Keller,²⁸ and others, established the location of the central heat-dissipation mechanism in experimental animals in the preoptic and supraoptic regions, and heat-conservation and heat-production mechanism in the more caudolateral portion of the hypothalamus. The same general plan applies to man (Alpers,³ Beaton and Herrmann,⁸ Davison,¹⁶ Zimmerman⁷¹). In an intensive study of the hypothalamus in 13 cases of heat stroke in relatively old persons afflicted with various chronic diseases, Morgan and Vonderahe⁴⁰ found that acute cell alterations were mainly in cells of the tuberomammillary nucleus, and chronic changes, ascribed to pre-existing disease, in the nuclei tuberis laterales and the paraventricular nucleus. These authors attributed the hyperthermia to stimulative action induced by the acute cellular changes. They intimated that a predisposition to heat stroke existed by virtue of previous damage to nuclei concerned with heat dissipation. This is in accord with the observations of Morgan³⁹ on dogs and rabbits in which moderate hyperthermia (a rise of 1.2 to 5.4°F. in body temperature) was induced by the injection of typhoid or bronchisepticus toxin: chromatolytic changes were found in 60 per cent of cells of the tuberomammillary nucleus, in 15.8 per cent of those of the paraventricular nucleus, and in

12.6 per cent of those of the supraoptic nucleus.

Although we have no reason to doubt that the thermoregulatory mechanism in our cases was severely damaged functionally, we were unable to find significant anatomic change in the hypothalamus other than the hemorrhages.

Other Tissues of the Body

The pathologic changes in the thoracic and abdominal viscera and elsewhere in the body were numerous and diverse. Evidences of acute circulatory failure, such as hemorrhage, edema, and vascular engorgement, were observed in virtually all cases regardless of the duration of illness. Parenchymal damage, on the other hand, was present only in certain cases, but tended to be more severe the longer the survival.

HEMORRHAGES. Hemorrhages constituted one of the most striking features at autopsy. They were petechial or of greater scope regardless of their location. The approximate incidence of hemorrhage in the 125 cases is shown in Table XV. The longer the patients' survival, the wider the dissemination of hemorrhage. Thus, when death occurred within 12 hours after the onset, the different locations of hemorrhage averaged 4.4 whereas when death occurred after 48 hours or more the average was 5.3. No correlation could be made between dissemination of hemorrhages and blood pressure levels. Hemorrhage was as frequent in cases in which the diastolic pressure was below 50 as when it was above. In our collection of 125 cases several which were parallel clinically showed the widest variation in the number of sites of hemorrhage.

Hemorrhages were absent in only 3 of our cases. In each of these the only known common factor was that of comparatively low temperature. Thus, in 2 (Cases 100855 and

FIG. 21. Duration of illness, 5 hours. Admission T. 109°F.; B. P. not recorded. Diffuse hemorrhage is present in the leptomeninges. $\times 75$. AIP Acc. 88639.

FIG. 22. Duration of illness, 4 hours. Admission T. 111°F.; B. P. 80/55. Coalescing petechial hemorrhages predominate in the paraventricular nucleus of the hypothalamus. (F) fornix; (3V) third ventricle. Cresyl violet stain. $\times 40$. AIP Acc. 112744.

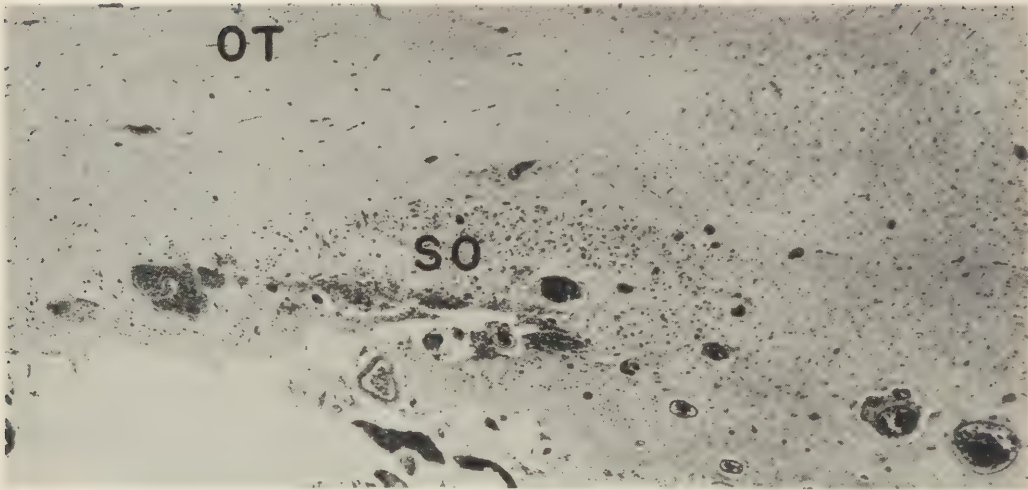


FIG. 23

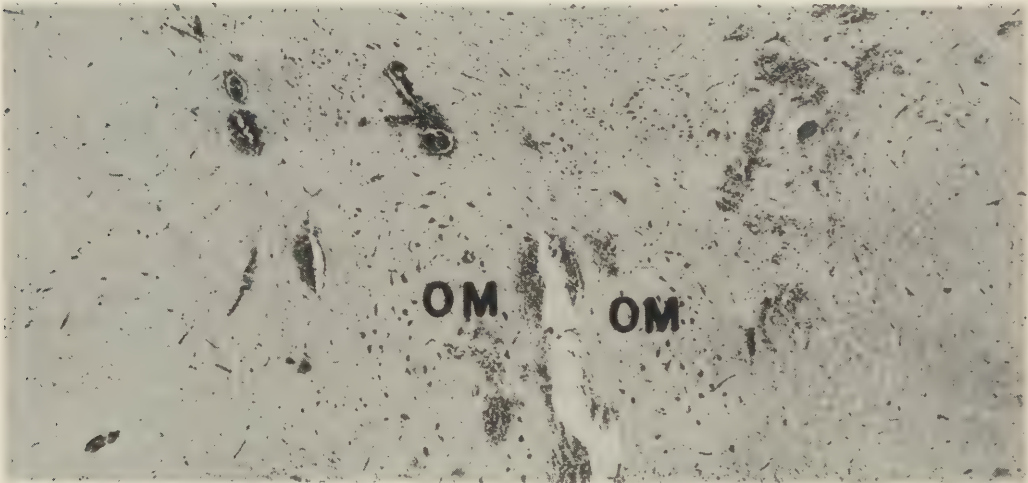


FIG. 24

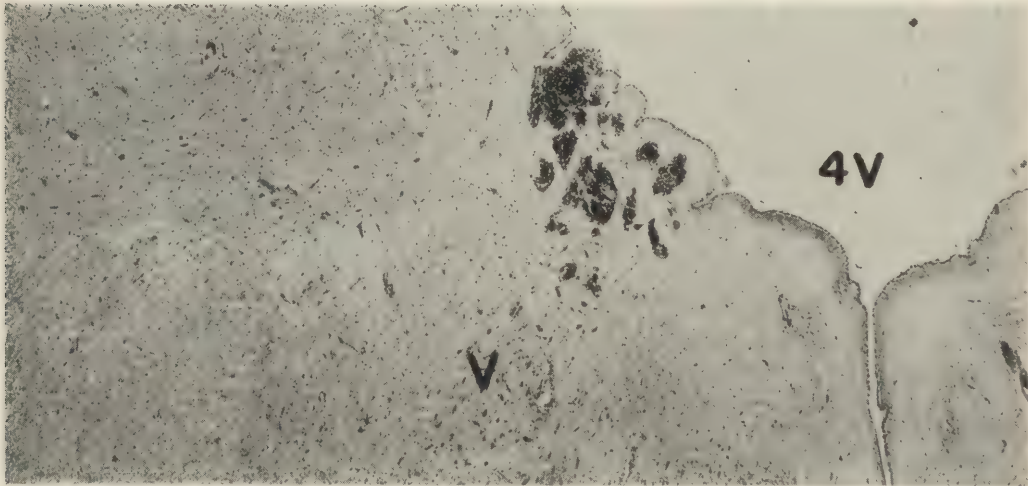


FIG. 25

101159), of less than 24 hours' duration, the temperatures were 101° and 97°F. respectively, while in the other (Case 98160), of several days' standing, the temperature remained below 104°F. until terminally. The blood pressures in the first 2 cases were too low to read whereas that of the third is not known.

SEROUS CAVITIES. Transudates into one or more serous cavities occurred in 33 of the series, being equally frequent in acute and chronic cases. Pericardial fluid in excess was observed in 20 cases; the fluid was blood-tinged in 4, bloody in 2, and straw-colored in the remainder, the amount ranging between 25 and 75 cc. with an average of 40 cc. In 3 other instances there was a slight amount of bloody fluid in the pericardial sac. Where pericardial blood existed there were always numerous petechial or ecchymotic hemorrhages of the serous membrane. The pleural cavities were second only to the pericardium as sites of transudate. The fluid, usually about equal in amount on the two sides, was serous in 9 instances, blood-tinged in 7, and bloody in 3. The range was between 50 and 2100 cc. with an average of 330 cc. Least often affected was the peritoneal cavity, which contained serous fluid in 3 cases and blood-tinged in 2, the amount ranging between 40 and 300 cc. with an average of 185 cc. In 2 instances in which large subserosal hematomas (6 and 10 cm. in diameter) were found there was no free blood in the peritoneal cavity.

HEART. No disproportion in the relative sizes of the heart chambers could be seen in the majority of cases. In 23 the right side, especially the auricle, was dilated, and in 2 the left ventricle. The heart was in complete

systole in 4 cases. Frequently the muscle was described as flabby.

Hemorrhages were common (Table XVI). They were observed as often in cases of short as of long duration. Those in the subepicardial tissue, usually petechial (Fig. 28),

TABLE XV
THE INCIDENCE OF HEMORRHAGE IN 125 FATAL
CASES OF HEAT STROKE

Skin.....	38
Conjunctivae.....	12
Meninges.....	20
Brain.....	65
Pleurae.....	33
Lungs.....	73
Epicardium.....	76
Endocardium.....	65
Heart Muscle.....	24
Peritoneum.....	73
Gastro-intestinal Tract.....	49
Spleen.....	15
Pancreas.....	8
Peri-adrenal.....	20
Renal Pelvis.....	10
Urinary Bladder.....	5
Others*.....	14

* These include hemorrhages into subcutaneous tissue, skeletal muscle, kidney parenchyma, ureters, mucous membranes of nose and mouth, thymus, liver, neurohypophysis, choroid plexus, wall of gall bladder, and peritracheal, peribronchial, perithyroid and peri-aortic tissues.

tended to be concentrated at the base of the heart, especially in the vicinity of the anterior longitudinal sulcus, and they sometimes involved the parietal pericardium as well. Several relatively large subepicardial extravasations of blood were found, the largest measuring 4 x 3 cm. Occasionally, confluent hemorrhages covered all surfaces of the heart. The

FIG. 23. Duration of illness, 8 hours. Admission T. 109°F.; B. P. 60/o. The supraoptic nucleus (SO) and vicinity exhibit perivascular and diffuse hemorrhage. (OT) optic tract. Cresyl violet stain. X40. AIP Acc. 99612.

FIG. 24. Duration of illness, 35 hours. Admission T. 106°F.; B. P. 100/70. There are petechial hemorrhages and vascular engorgement of the periaqueductal gray matter and the oculomotor nuclei (OM). Cresyl violet stain. X40. AIP Acc. 110465.

FIG. 25. Duration of illness, 5 hours. Admission T. 109°F.; B. P. not recorded. Petechial hemorrhages present in the floor of the fourth ventricle (4V) are in the vicinity of the dorsal efferent nucleus of the vagus (V). Cresyl violet stain. X40. AIP Acc. 88639.

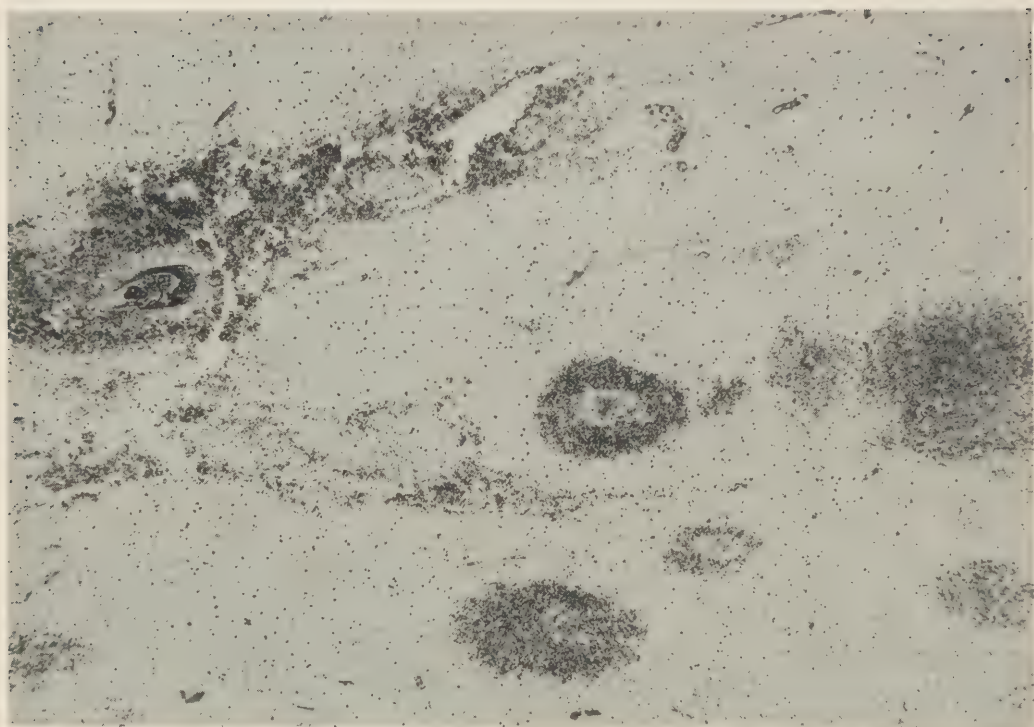


FIG. 26



FIG. 27

TABLE XVI

DATA ON NINETEEN FATAL CASES OF HEAT STROKE IN WHICH LOWER NEPHRON NEPHROSIS WAS OBSERVED

AIP Acc.	Duration of Illness (Hrs.)	Degree of Hb. Nephrosis			Blood Pressure	NPN (mg. %)	Transfusion		Centro- lobular Necrosis of Liver
		Mild	Mod.	Severe			Plas- ma	Blood	
88640	8½	+	o	o	90/0, 118/70	—	+	o	o
85875	12½	+	o	o	—	—	+	o	o
101019	13½	+	o	o	100/60	—	o	+	o
83038	15½	+	o	o	—	—	o	o	o
101442	18	o	+	o	80/20, 120/60, 80/50	—	+	o	o
98176	19	o	+	o	122/70	—	o	o	o
98213	23½	+	o	o	110/60	—	o	o	o
102099	24	o	+	o	80/30, 60/40	—	o	o	o
99625*	24	o	+	o	104/40	—	+	o	o
97555	26	o	+	o	60/40, 110/70, 60/40	45	+	o	o
84111	26	+	o	o	100/20, 120/60	—	o	o	o
97554	34	o	+	o	136/80, 86/40	48	+	o	o
97148	35	o	o	+	150/110, 60/40	58	o	o	+
113428	36	o	o	+	78/50, 105/65	—	o	o	+
115686	39	o	o	+	135/65, 130/90	49	o	o	o
98544	72	o	o	+	98/60, 100/30, 120/60	—	o	o	+
96554	72	o	o	+	102/64	—	+	o	+
95093	96	o	o	+	50/0, 102/68, 50/20	—	+	+	+
120161	249	o	o	+	100/60, 114/66, 110/90	133, 231, 229, 213†	+	o	o

* This is the only case of the series in which sulfonamides were administered.

† Urea nitrogen values were also elevated: 25.9, 37.5, 66.0 and 46.8 mg. %.

subendocardial tissue was somewhat less frequently the seat of hemorrhage. The site of predilection was the left side of the interventricular septum, but in numerous instances the adjoining left ventricular wall, including the papillary muscles, was involved. Leaflets of the aortic, mitral and tricuspid valves contained petechiae occasionally, and larger hemorrhages were present in the subendocardium (Fig. 29) in 10 cases. In one case extravasation of blood had undermined almost all of the endocardium of the left ventricle, and in another, hemorrhage reddened an entire tricuspid leaflet, but most of the ecchymoses were in the region of the bundle of His. This concentration of endocardial hemorrhages has previously been emphasized by Wilson.⁶⁵

Hemorrhage into cardiac muscle, especially that of the left ventricle, occurred in 24 instances. Occasionally a massive extravasation of blood was found in the wall of the heart (Fig. 30).

Sections of heart stained by the Bodian method revealed degenerative changes in 13 of the 27 cases in which the illness lasted more than 24 hours; the lesions were minor in 6 and major in 7. Degeneration was also seen in approximately one-third of the cases of shorter duration, and was minor in all except 2. The lesions were either focal and well circumscribed, or diffuse and patchy. Usually they were small (Fig. 31), occasionally large (Fig. 32). Focal necrosis was evident in cases in which death occurred as early as 6 hours

FIG. 26. Duration of illness, 4 days. T. 97, 107°F.; B. P. 40/0. Ring hemorrhages surround thrombosed vessels in the cerebral white matter ('brain purpura'). Cresyl violet stain. $\times 70$. AIP Acc. 101661.

FIG. 27. Duration of illness, 12 hours. Perivascular foci of rarefaction are scattered throughout the cerebral white matter. Hematoxylin and eosin stain. $\times 70$. AIP Acc. 95285.

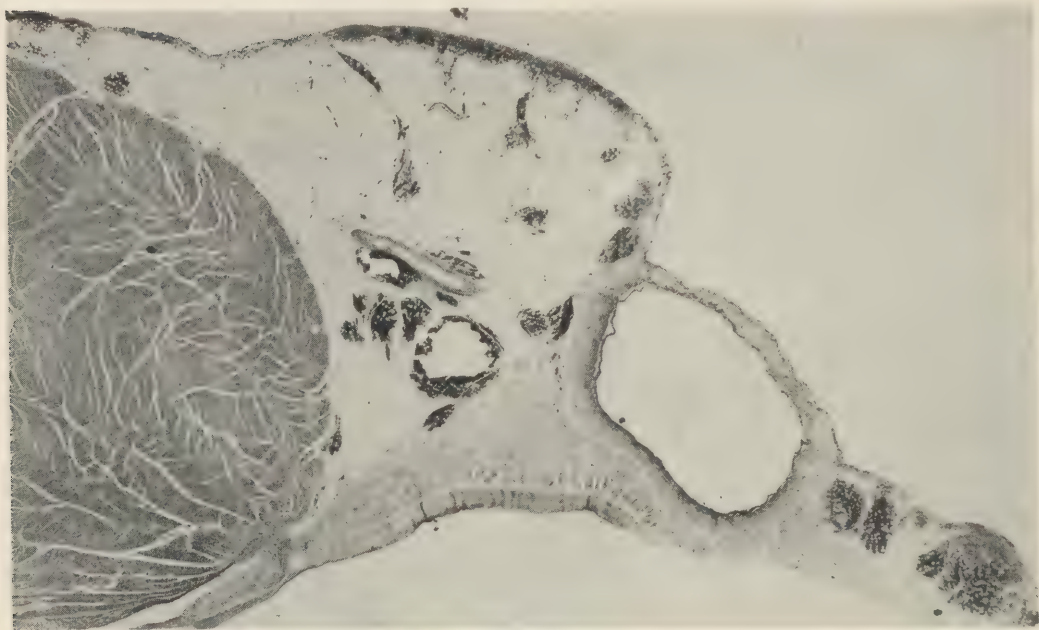


FIG. 28

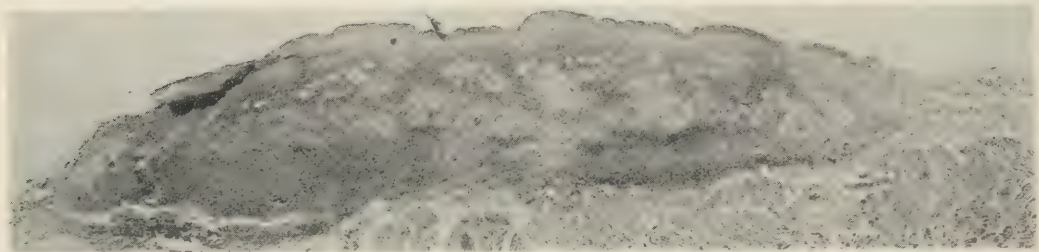


FIG. 29

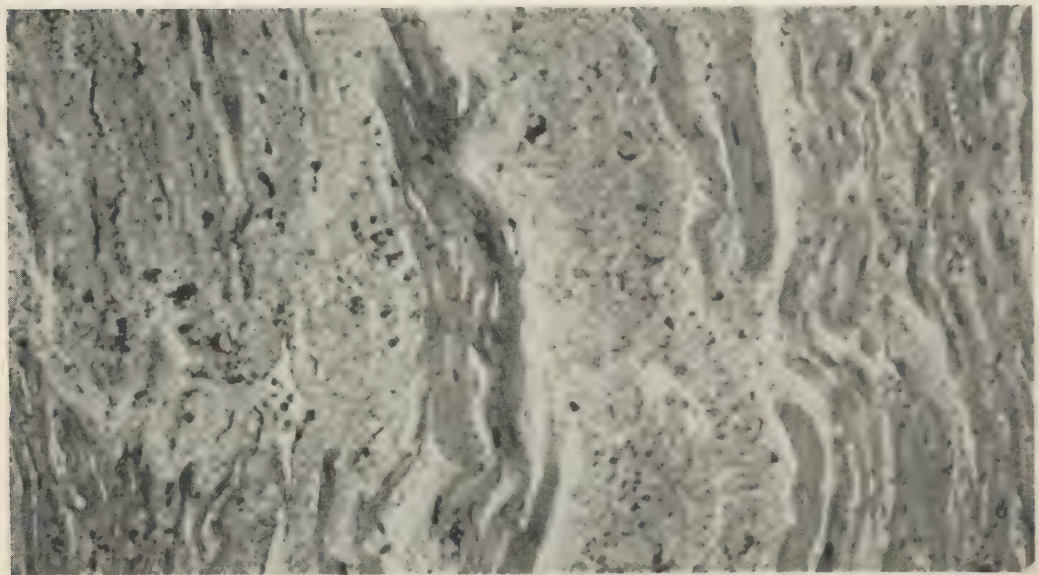


FIG. 30

after onset (Fig. 33). The degenerative change was often decidedly irregular, imparting to the muscle fibers a moth-eaten appearance (Fig. 34). In some of the chronic cases, and in an occasional acute one, several contiguous segments of muscle fibers were shrunken, devoid of nuclei and entirely amorphous (Fig. 35). Sometimes only a part of a muscle segment adjoining an intercalated disk was affected (Fig. 36). Fragmentation or rupture of muscle fibers (Fig. 38) was conspicuous in well over one-fourth of the cases.

When sections of the heart from representative cases were stained for fat a somewhat greater incidence of degenerative changes was disclosed than by the Bodian method. Significant fatty change in cardiac muscle was evident in cases in which the span of illness was as short as $3\frac{1}{2}$ hours. A section of the heart from a case of 10 hours' duration is shown in Figure 37.

LUNGS. The lungs were the seat of hemorrhage in 73 of the series. Gross observation revealed hemorrhages of three sorts: petechial, which were widespread and usually associated with pleural petechiae; ecchymotic, which were wedge-shaped and discrete and frequently subpleural in location; and massive. In most of these cases the lungs were literally saturated with blood. The hemorrhage was usually limited to the lower lobes of both lungs, but frequently it involved the lower portions of the middle and upper lobes as well. That edema was almost invariably associated with hemorrhage was apparent from the abundant frothy hemorrhagic fluid which the lungs and bronchial tree yielded on section. The high degree of hemorrhage and edema was reflected in the weights of the lungs: that of the two together varied from 640 to 2360 gm., the average being 1315 gm., and in

no case was within normal limits.

Microscopic examination confirmed the gross findings. In virtually all cases there was intense vascular congestion. Where hemorrhage existed, it usually filled or partly filled individual alveoli (Fig. 39). Wedge-shaped, neatly circumscribed ecchymoses were usually found to be hemorrhagic infarcts (Fig. 40) which apparently were secondary to circulatory stasis with venous thrombosis. Sometimes there was hemorrhage without edema (Fig. 41). Perivascular hemorrhage was rare. In the portions of the lung free from hemorrhage and edema the air sacs were considerably distended; series of them were often ruptured (Fig. 40).

Lobular pneumonia was found in 16 cases in which survival was less than 48 hours and in 15 cases of longer duration. The overall incidence was about 25 per cent, in contrast to the 10 per cent reported by Reid.⁴³ Pneumonia in our group was observed as early as 8 hours after the onset of hyperthermia (Case 99825) and generally was restricted to hemorrhagic areas of the lung. It was severe in only 4, and was regarded as the chief contributor to death in 2 (Cases 94751 and 101118).

KIDNEY. The kidney usually was hyperemic no matter what the duration of the illness. In about half of the cases congestion was intense, involving medullary, cortical, and glomerular vessels alike. The glomerular tufts in many of the remaining cases were relatively less engorged than the capillary bed elsewhere. Ischemia of glomeruli, usually associated with a general decrease in the volume of blood in the kidney, was observed in 7 cases, in 3 of which there was hemoglobinuric nephrosis (Cases 97148, 97554 and 120161). The weights of the kidneys were above the recognized normal, the average combined weight being 360 gm., with a range between 200

FIG. 28. Duration of illness, 47 hours. The section in through the base of the left ventricle, the mitral valve, the left auricle and the main left coronary artery. The ventricular and auricular subepicardium contains numerous petechial hemorrhages, mostly perivascular. $\times 7$. AIP Acc. 97556.

FIG. 29. Duration of illness, 144 hours. A large ecchymosis is present in the subendocardial tissue of the left ventricle. $\times 20$. AIP Acc. 102705.

FIG. 30. Duration of illness, 19 hours. A widespread extravasation of blood in the myocardium disrupts many of the muscle fibers. $\times 190$. AIP Acc. 86244.

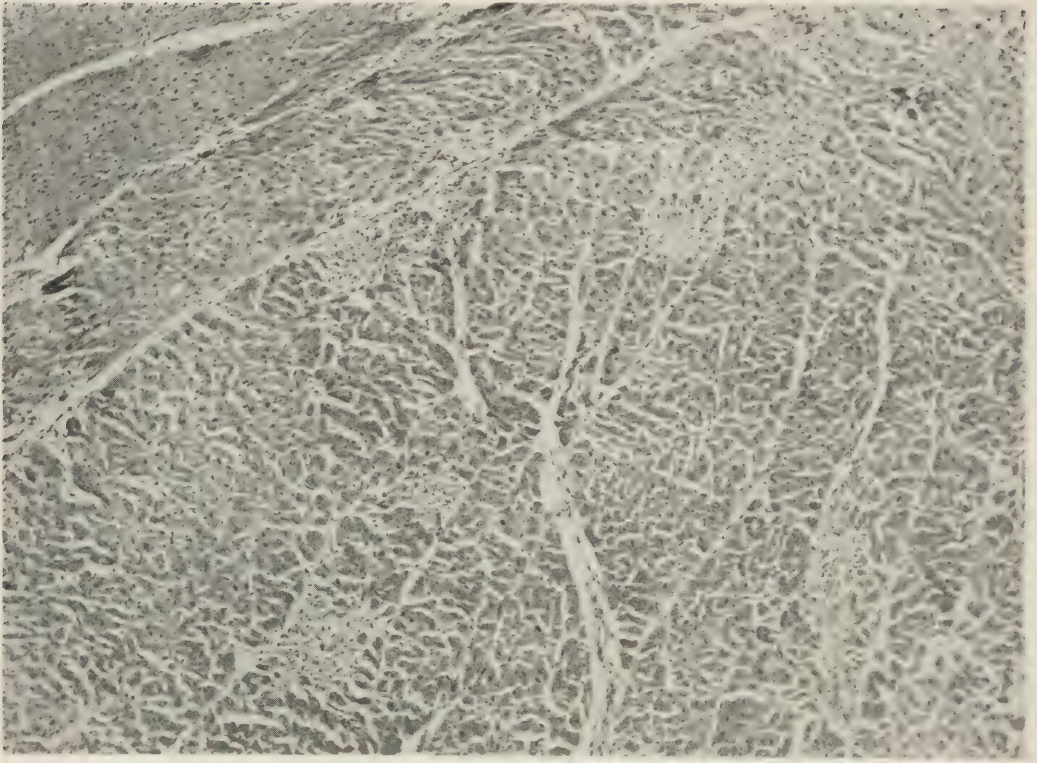


FIG. 31

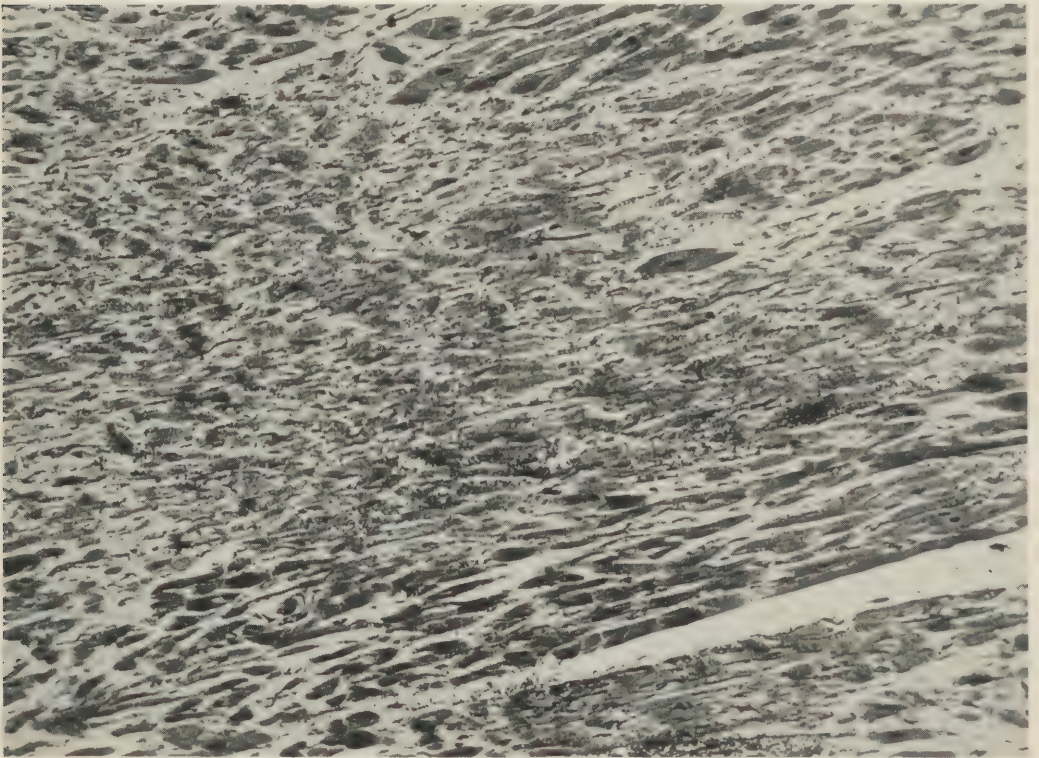


FIG. 32

and 600 gm. In three-fourths of the cases the weights were more than 300 gm.

Hemorrhages, usually petechial but occasionally ecchymotic, were present in 20 cases: in pelvic tissue in 10, subcapsular in 9, and in interstitial tissues or tubules of the kidney in 3. Hemorrhages dotted the mucosa of the ureter in one, and were of greater scope in another (Fig. 42). The bladder was the seat of petechial or ecchymotic hemorrhage in 5 instances.

Parenchymal damage was scanty when the illness ran an acute course, but was more pronounced when the duration was longer. In approximately one-third of the cases in which the course was 24 hours or less a few pigmented casts were found in distal convoluted tubules, and in about one-ninth epithelial cells of distal convoluted tubules were in a state of early degeneration. A combination of the two was sometimes observed (Fig. 43). Changes sufficiently pronounced to warrant the diagnosis of lower nephron nephrosis ("hemoglobinuric nephrosis") were observed in 9 of this group of early cases (Table XVI). In most of these there were pigmented casts in distal segments of the nephron; in a few, foci of inflammatory cells were seen in the interstitial tissue, and occasionally necrosis of distal convoluted tubules dominated the picture (Fig. 44).

In cases of longer standing, the incidence of lower nephron nephrosis was considerably higher. Thus, of 27 cases in which survival was longer than twenty-four hours 10 exhibited this complication (Table XVI). Pigmented casts and disintegration of lining epithelium in the lower nephron (Fig. 45) were, in general, more widespread than in the cases of shorter duration; hyaline casts frequently were in profusion, collections of inflammatory cells (mostly lymphocytes) were sometimes observed in the interstitial tissue

(Fig. 46), and there was generally a proliferation of interstitial cells and an intertubular edema in cases of relative longstanding.

A survey of certain available clinical and laboratory data from the cases of lower nephron nephrosis (Table XVI) reveals that reduction in blood pressure and elevation of blood nonprotein nitrogen were usual. In a little less than half of the cases neither plasma nor whole blood transfusions were given. None of the patients received sulfonamides. Lobular necrosis of the liver was an associated finding in 5 of the more chronic cases.

LIVER. Like other organs, the liver usually was congested and weighed more than normal. The average weight was 1790 gm., the range being between 1200 and 3260 gm. Perisinusoidal edema was frequent, and on occasion severe (Fig. 47). In cases in which survival was less than 30 hours there was no evidence of damage to parenchymal cells. Thirty-one hours after onset was the soonest centrilobular necrosis was detected. In the 12 cases in which necrosis was present (Table XVII) the degree of damage ranged from moderate to severe (Figs. 48 and 49). Frequently the liver was relatively ischemic. Dissociation of liver cords was observed in several of the chronic cases and in a few of the acute ones. Kupffer cells remained unaltered.

Reference to clinical and laboratory data in the 12 cases in which the liver underwent necrosis (Table XVII) reveals that lower nephron nephrosis was present in 8. Transfusion of plasma or blood had been given in 6. Jaundice became manifest in some cases of longer standing, and the icterus index was elevated in 2 cases in which jaundice was not detected.

ADRENAL. In most of the cases of brief duration there was engorgement of sinusoids, while in those of longer duration a relative ischemia was frequent. Hemorrhage was rare,

FIG. 31. Duration of illness, 72 hours. A number of miliary infarcts are visible in heart muscle, the fibers in these foci being uniformly disintegrated. Bodian stain. $\times 70$. AIP Acc. 98544.

FIG. 32. Duration of illness, 130 hours. Section through the left ventricle of the heart discloses a relatively large area of necrosis associated with moderate extravasation of blood. Bodian stain. $\times 110$. AIP Acc. 115309.

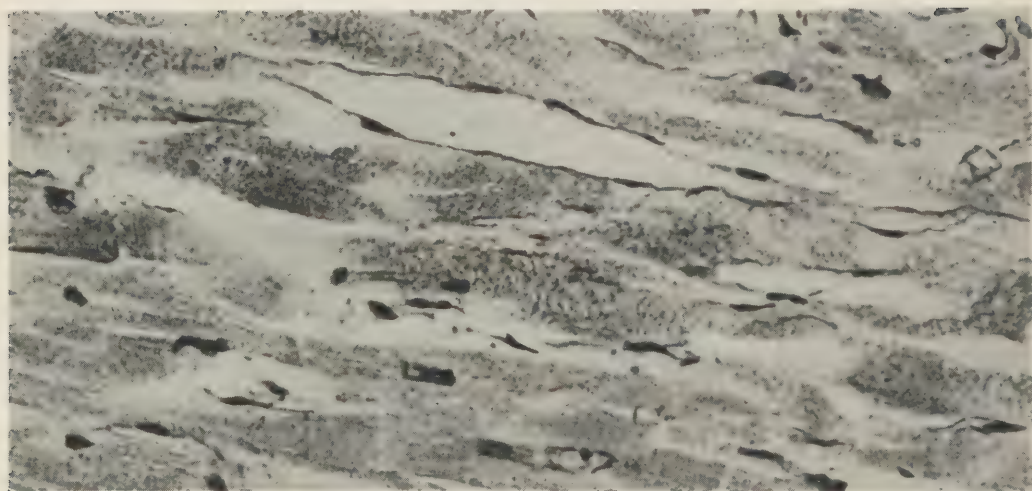


FIG. 33. Duration of illness, 6 hours. In focal areas of cardiac degeneration many of the cross-striations have lost their identity, and those that remain consist of dispersed granules. Capillary engorgement is notable. Bodian stain. $\times 500$. AIP Acc. 98519.



FIG. 34. Duration of illness, 168 hours. The degenerative changes in the cardiac muscle are irregular, giving a moth-eaten effect. Bodian stain. $\times 500$. AIP Acc. 98160.



FIG. 35. Duration of illness, 96 hours. Disintegration is present over several contiguous segments of cardiac muscle. Such areas were numerous in this case. Bodian stain. $\times 350$. AIP Acc. 95093.

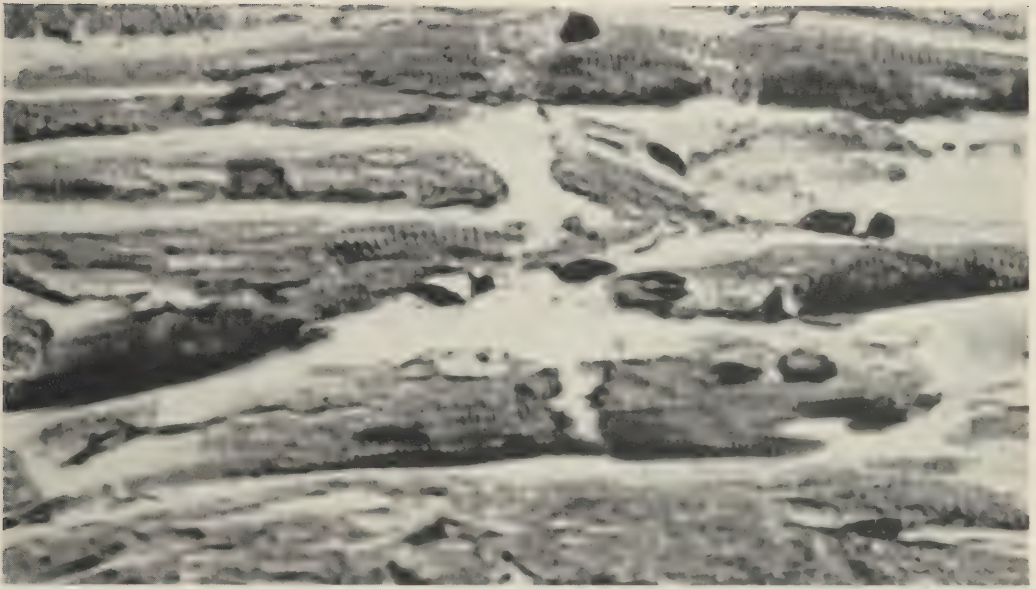


FIG. 38. Duration of illness, 9 hours. There is frank rupture of degenerated muscle fibers. Bodian stain. $\times 850$. AIP Acc. 110273.

being minimal and confined to the junctional zone of medulla and cortex in only two. Pericapsular hemorrhage, on the other hand, occurred in 20 instances (Table XV). Perisinusoidal edema was infrequent. The lipid content of cells of the adrenal cortex was within normal limits in most of the cases in which survival was less than 24 hours, but

generally was depleted in cases of longer duration. In some of the more chronic cases the cytoplasm of the cells of the adrenal cortex had a compactness similar to that of liver cells.

Degenerative changes in the adrenal cortex were of relatively minor degree. In about 12 of the series, especially in those in which the illness ran an acute course, the cords of the

TABLE XVII

DATA ON 12 FATAL CASES OF HEAT STROKE IN WHICH CENTROLOBULAR NECROSIS OF THE LIVER WAS OBSERVED

AIP Acc.	Duration of Illness (Hrs.)	Degree of Necrosis			Blood Pressure	Jaun- dice	Icterus Index	Transfusion*		Lower Nephon Nephro- sis
		Mild	Mod.	Severe				Plas- ma	Blood	
95887	31	o	+	o	—	?	—	o	o	o
97148	35	o	+	o	150/110, 60/40	?	—	o	o	+
110465	35	o	o	+	110/70	o	—	+	o	+
113428	36	+	o	o	78/50, 105/65	o	31.8	o	o	+
94751	60	+	o	o	125/70, 108/60	+	—	o	+	o
98544	72	o	o	+	98/60, 100/30, 120/60	o	—	o	o	+
96554	72	o	o	+	102/64	o	60.0	+	o	+
101158	72	o	o	+	110/70	+	—	+	o	+
95093	96	o	o	+	50/0, 102/68, 50/20	o	—	+	+	+
132693	104	o	+	o	82/60	+	—	o	o	o
115309	130	o	o	+	142/30, 82/52, 120/80	+	—	o	o	+
118078	276	o	+	o	80/40, 98/60, 130/78	?	16.0	+	o	o

* None of the patients in this series received sulfonamides.

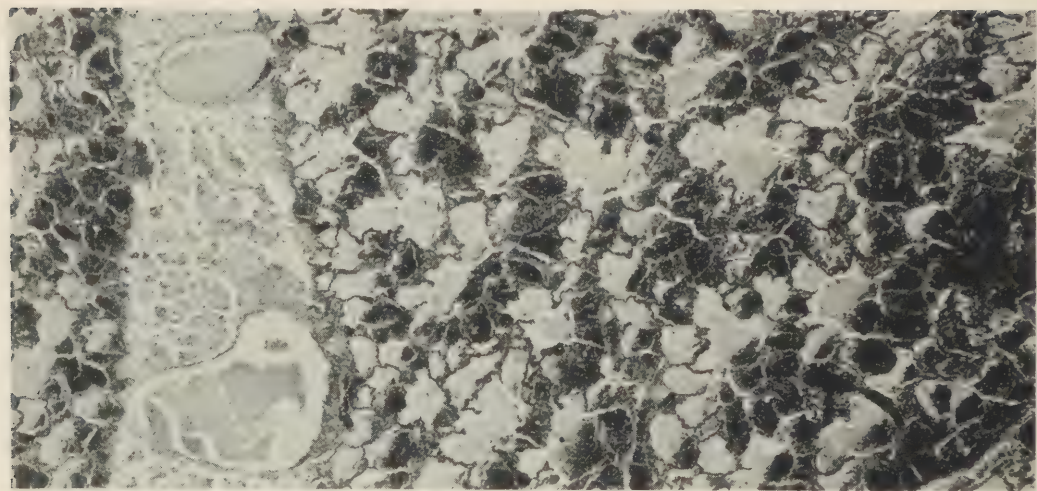


FIG. 39

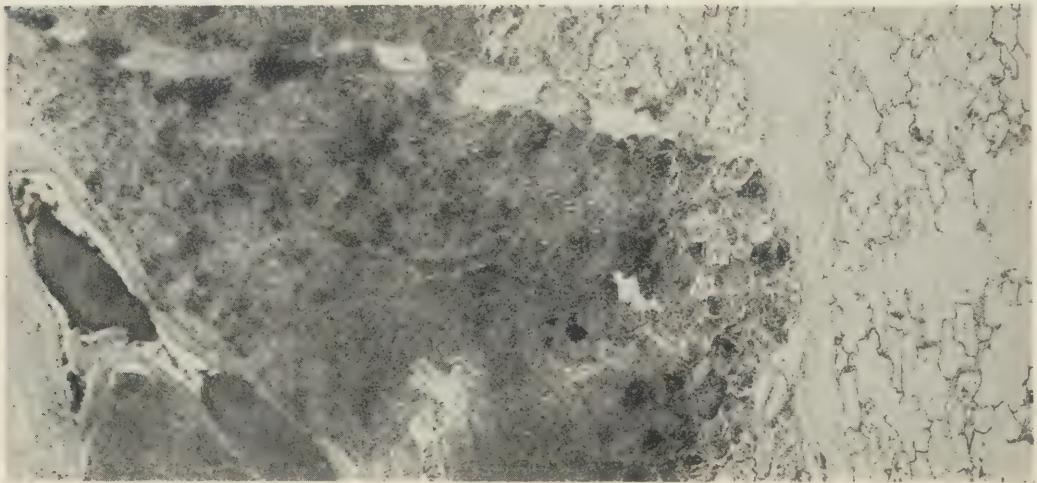


FIG. 40

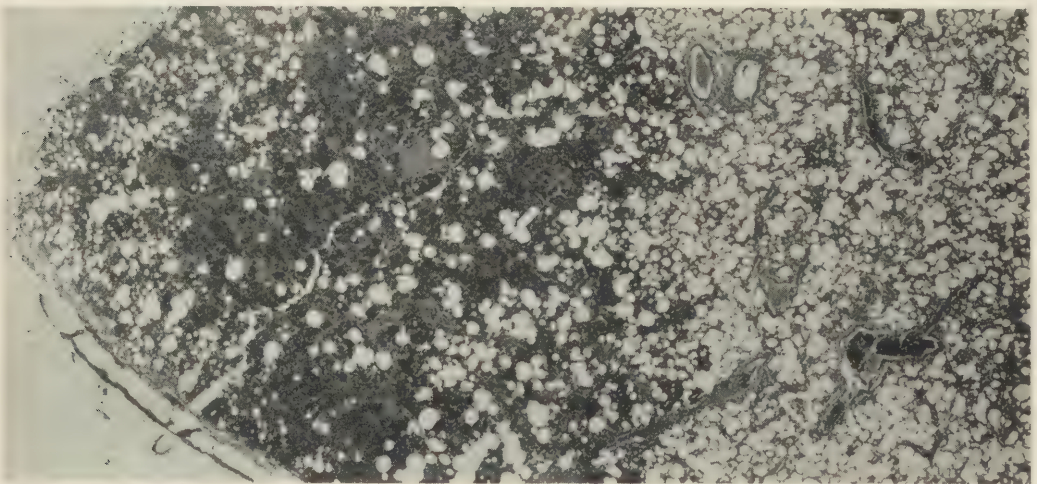


FIG. 41

zona fasciculata and sometimes the ovoid groups of cells of the zona glomerulosa showed the "tubular degeneration" originally described by Rich⁴⁴ in fulminating infectious diseases: it was as though intercellular adhesion had been lost, causing apposing columns or groups of cells to spring apart, converting them into "tubules" (Fig. 50). Actual necrosis of cells of the adrenal cortex was observed only in cases in which survival was more than 24 hours. Altogether 12 of the 28 cases in the "chronic" group showed this change. Usually the necrosis was focal and was limited to the zona fasciculata, as has been noted also in hyperthermia by Kopp and Solomon.³⁰ In some instances the cells undergoing disintegration were greatly shrunken, distorted, and disarranged, and were surrounded by cells having the appearance of macrophages (Fig. 51). Relatively large areas of degeneration of the zona fasciculata were present in only one case (Fig. 52). Occasionally the degenerate cells had disappeared from the fibrous stroma (Fig. 53). Except for congestion, which varied in degree, the adrenal medulla appeared normal in every case.

BONE MARROW. Histologic study of bone marrow was limited to 15 cases. Congestion was a prominent feature in all. Of the various elements of the bone marrow, the megakaryocytes suffered by far the most. In only 3 cases were the megakaryocytes undamaged; in 2 of these the survival period was exceedingly short (2 hours), and in the other the patient's temperature was subnormal (Table XVIII). The changes in megakaryocytes consisted of severe pyknosis of nuclei, karyorrhexis, and disappearance of nuclei (Fig. 54 and 55). Severe degenerative changes in megakaryocytes were evident as early as 6 hours after onset of hyper-

thermia. In approximately half of the 15 cases there was a reduction in the number of megakaryocytes. Regeneration was apparent in 3 instances, numerous megakaryoblasts being in evidence (Fig. 56). Depletion of cells of the granulocytic and erythrocytic series was observed when survival was 35 hours or more, but in only one was the loss of cells severe (Fig. 57). Inasmuch as bone marrow changes of this severity were not seen in the controls, which included cases of anoxic anoxia (Titrud and Haymaker⁵⁶), they were believed to be due essentially to excessive heat.

SPLEEN. The only significant finding in the spleen was that of congestion, and in 15 cases small hemorrhages. The weight of the spleen was somewhat increased in approximately one-seventh of the cases, the average of this group being 290 gm.

GASTRO-INTESTINAL TRACT. The vessels throughout the gastro-intestinal tract were engorged in virtually all the cases, with hemorrhages usually punctate and confined to the mucosa in 49 (Fig. 58). Edema of the submucosa was a common finding. Ulceration of the stomach and duodenum was observed only once (Case 115309), the tarry black mucoid material in the entire gastro-intestinal tract at autopsy indicating that the ulceration had been present during life.

REMAINING TISSUES. No significant lesions were observed except as listed in Table XV.

DISCUSSION OF THE PATHOLOGIC CHANGES IN TISSUES OTHER THAN THE BRAIN. Most of the lesions apart from those in the brain can be attributed to the anoxia and circulatory collapse incident to shock. Thus, hemorrhages, serous transudates, focal myocardial degeneration, pulmonary infarcts

FIG. 39. Duration of illness, 18 hours. Hemorrhage or edema fluid, or both, fill virtually all alveolar sacs of the lung. The partially adherent interlobar cleft is edematous, and persistent mesothelial-lined spaces are filled with transudate. $\times 30$. AIP Acc. 101442.

FIG. 40. Duration of illness, 12 hours. The section presents a hemorrhagic infarct of the lung which apparently is secondary to stasis venous thrombosis. A beginning lobular pneumonia is present. Uninvolved portions are emphysematous. $\times 25$. AIP Acc. 118077.

FIG. 41. Duration of illness, 2 hours. Part of the section of the lung presents a diffuse hemorrhage whereas the remainder is relatively normal. $\times 10$. AIP Acc. 149848.

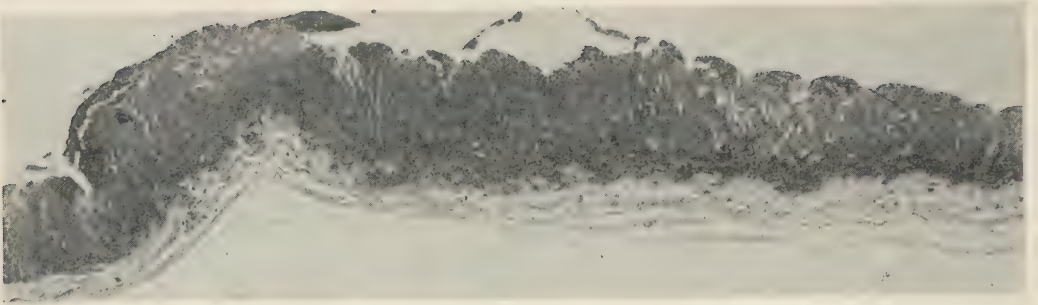


FIG. 42

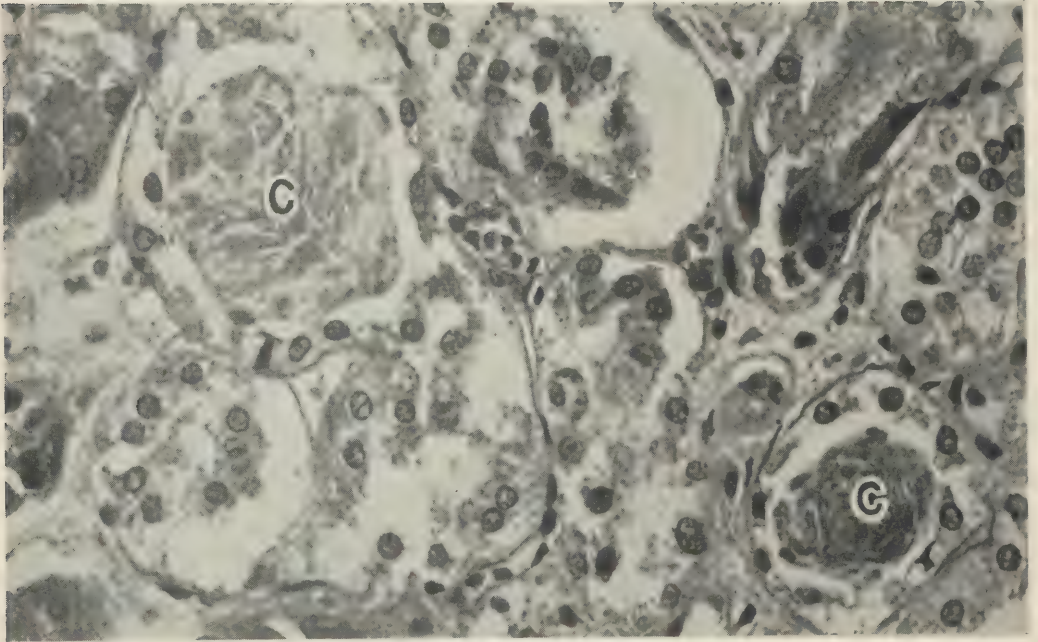


FIG. 43

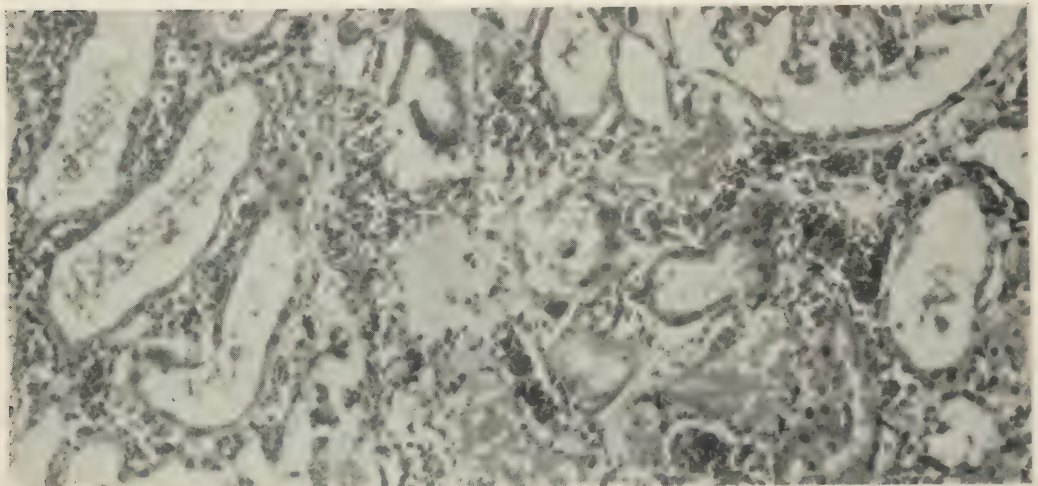


FIG. 44

of the stasis type, centrolobular necrosis of the liver, tubular degeneration and necrosis in the adrenal cortex, and lower nephron nephrosis have all been observed in shock developing from a variety of causes. It is likely that the liver damage can be attributed in part to hyper-

stroke. We gained the impression that the extent of hemorrhage was greater than that ordinarily seen in shock due to other causes. Furthermore, although there seemed to be some correlation between hemorrhage in the brain and low blood pressure indicative of

TABLE XVIII
FINDINGS IN THE BONE MARROW IN 15 FATAL CASES OF HEAT STROKE

AIP Acc.	Duration of Illness (Hrs.)	Maximum Temp. (° F.)	Blood Pressure	Megakaryocytes			Platelet Count	Depletion of Cells other than Megakaryocytes	Degree of Hemorrhage†
				Normal	Degeneration*	Regeneration*			
94560	2	108.8	50/0	+	o	o	—	o	+++
97599	2	109	80/0	+	o	o	—	o	++
99445	6	106.6	—	o	+++	o	—	o	+
117740	7	110	120/90	o	++	o	120,000	o	+++
101829	7½	108	80/40, 100/60, 60/40	o	+++	o	—	o	+++
101159	12	97	90/0	o	o	o	—	o	o
118077	12	110	100/60, 108/56, 70/50	o	+	o	40,000	o	+++
97555	26	109.2	60/40, 110/70, 60/40	o	+	++	—	o	++
86617	32	106.4	80/60	o	+++	+	—	o	+++
97148	35	107.2	150/110, 60/40	o	++	o	—	+	++
110465	35	106	110/70	o	++	o	—	+	++
97556	47	109	80/50, 100/70, 135/85	o	+	+++	—	++	+
96554	72	108	102/64	o	+++	+	—	+	+++
98544	74	107.8	98/66, 100/30, 120/60	o	++	o	—	+++	+++
118078	276	110	80/40, 98/60, 130/78	o	++	o	92,000 31,000 66,000 130,000 260,000	+	++++

* +, mild; ++, moderate; +++, severe.

† The degree of hemorrhage is based on the number of sites of hemorrhage: +, 1 to 2 sites; ++, 3 to 4; +++ 5 to 7; +++++, more than 7.

thermia inasmuch as disturbances in liver function occur regularly after fever therapy (Wallace and Bushby⁶⁰).

It would appear that some factor other than shock also contributes to hemorrhage in heat

stroke, the same could not be said for the tissues at large. We believe that the other factor concerned is that of impaired coagulation of the blood. Wilson and Doan⁶⁷ noted a reduction in platelets and prothrombin time in

FIG. 42. Duration of illness, 18 hours. The mucosa of the ureter is the seat of widespread hemorrhage, and the wall is very edematous. $\times 15$. AIP Acc. 118655.

FIG. 43. Duration of illness, 12 hours. Haem casts (C) occupy two of the distal convoluted tubules of the kidney. The cytoplasm of the epithelial cells is fragmented and some of the nuclei are pyknotic. The capillaries are not engorged. $\times 550$. AIP Acc. 101159.

FIG. 44. Duration of illness, 24 hours. Autopsy was performed 10 hours after death. A number of the distal convoluted tubules are necrotic. Proximal convoluted tubules are dilated and the epithelial cells are flattened but well preserved. Congestion is of lesser degree in glomerular tufts than in intertubular vessels. $\times 280$. AIP Acc. 99625.

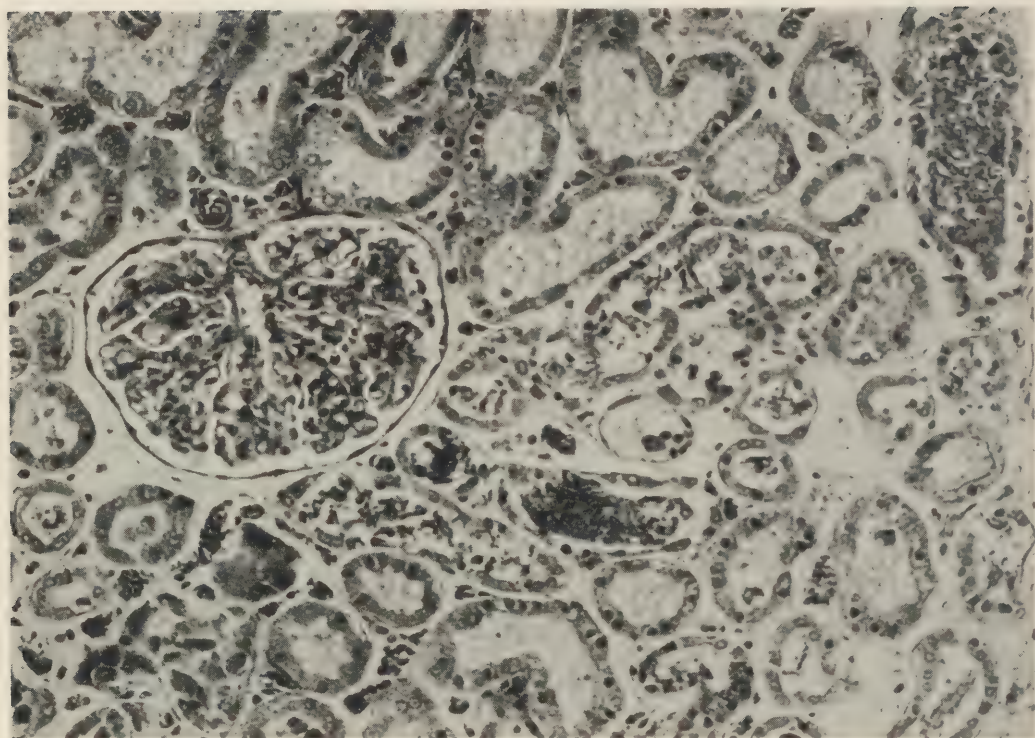


FIG. 45. Duration of illness, 34 hours. Autopsy was performed 12 hours after death. Two of the distal convoluted tubules contain well formed pigmented casts while in others there is considerable pigmented debris. Degenerative changes are present in the epithelial cells of these tubules. Below the glomerulus, two of the distal convoluted tubules are undergoing disintegration. Intertubular capillaries are somewhat engorged whereas the glomerulus is relatively ischemic. $\times 300$. AIP Acc. 97554.

patients during artificially induced fever, and the few cases in our series in which such data were available showed low platelet counts and prolonged bleeding times. The degenerative changes in megakaryocytes we regard as a direct effect of heat. It may be of some significance that of the 3 cases in our series which did not display hemorrhage even though the blood pressure in 2 was too low to read (not known in the third), the temperature in all was relatively low.

SUMMARY

This study is based on 125 fatal cases of heat stroke which occurred in the United States Army during the summer months of 1941 to 1944. All were from military installations in southern states of this country. In virtually all instances the soldiers were undergoing strenuous muscular exercise under conditions of high environmental temperature. Lack

of sufficient acclimatization seems to have been a predisposing factor in many of the cases.

An analysis of the clinical data establishes three categories of signs and symptoms: 1) those due primarily to hyperthermia, especially central nervous system manifestations; 2) those due secondarily to shock; and 3) those due to complications, such as lower nephron nephrosis and bronchopneumonia, arising during the course of the illness.

The clinical course was determined by the severity and duration of the primary symptoms, and was influenced largely by the factors of shock and complicating visceral disorders. Three types of course were observed: 1) an acute onset with early persistent coma or delirium; 2) an acute onset of early coma or delirium, with remission and late relapse; and 3) an insidious onset with a progressive course and late development of coma.

The duration of the disorder varied from

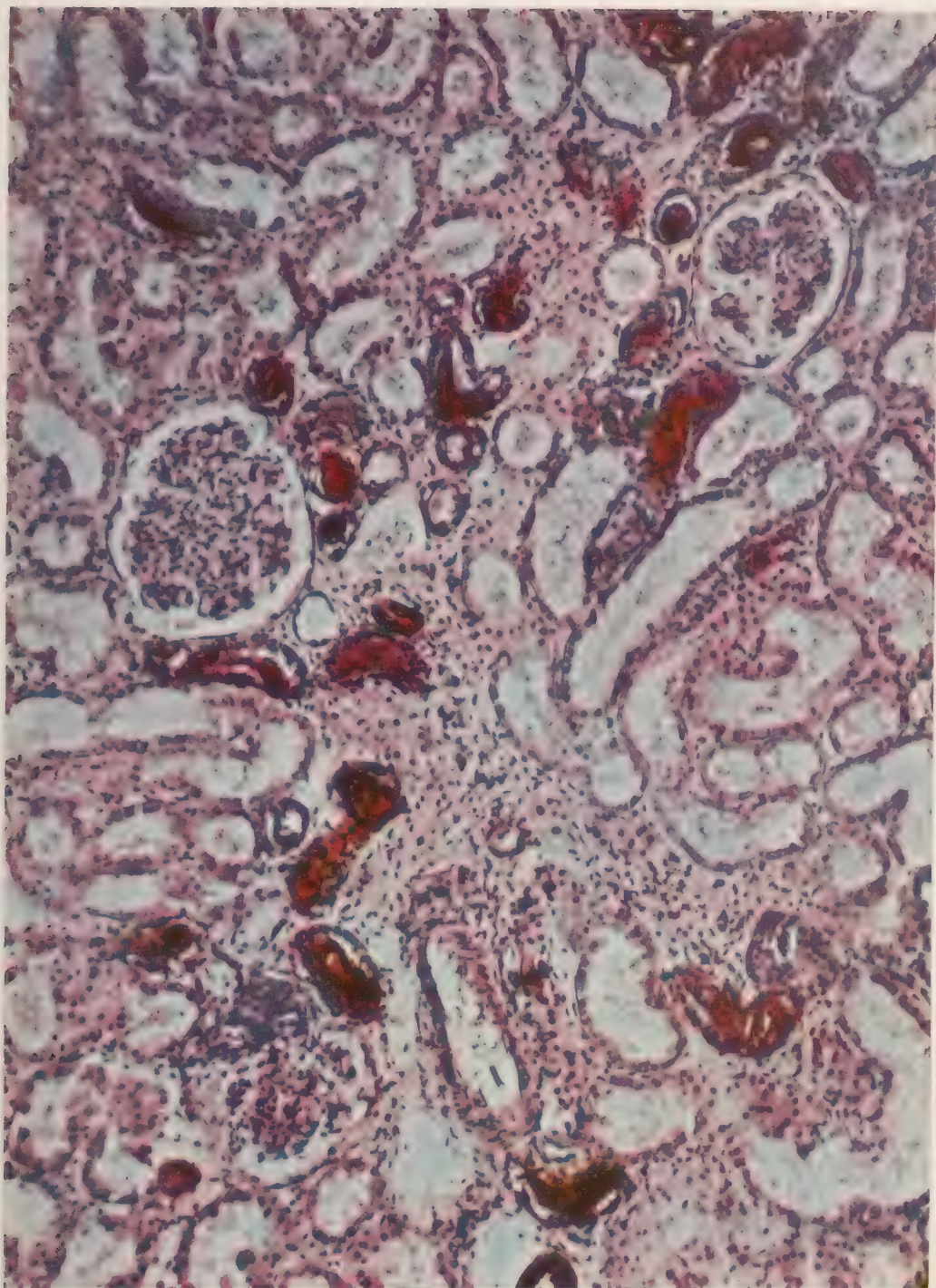


FIGURE 46. Duration of illness, 35 hours. There is well developed lower nephron nephrosis (hemoglobinuric nephrosis). The interstitial tissue is edematous, shows early stromal proliferation, and presents a sprinkling of inflammatory cells, mainly lymphocytes. Distal convoluted tubules and an occasional ascending limb contain casts: some are heme casts while others apparently are stained with bile pigment. (The patient had moderately severe centrilobular necrosis of the liver, but no evident jaundice.) The kidney as a whole was relatively ischemic. AIP Acc. 97148.

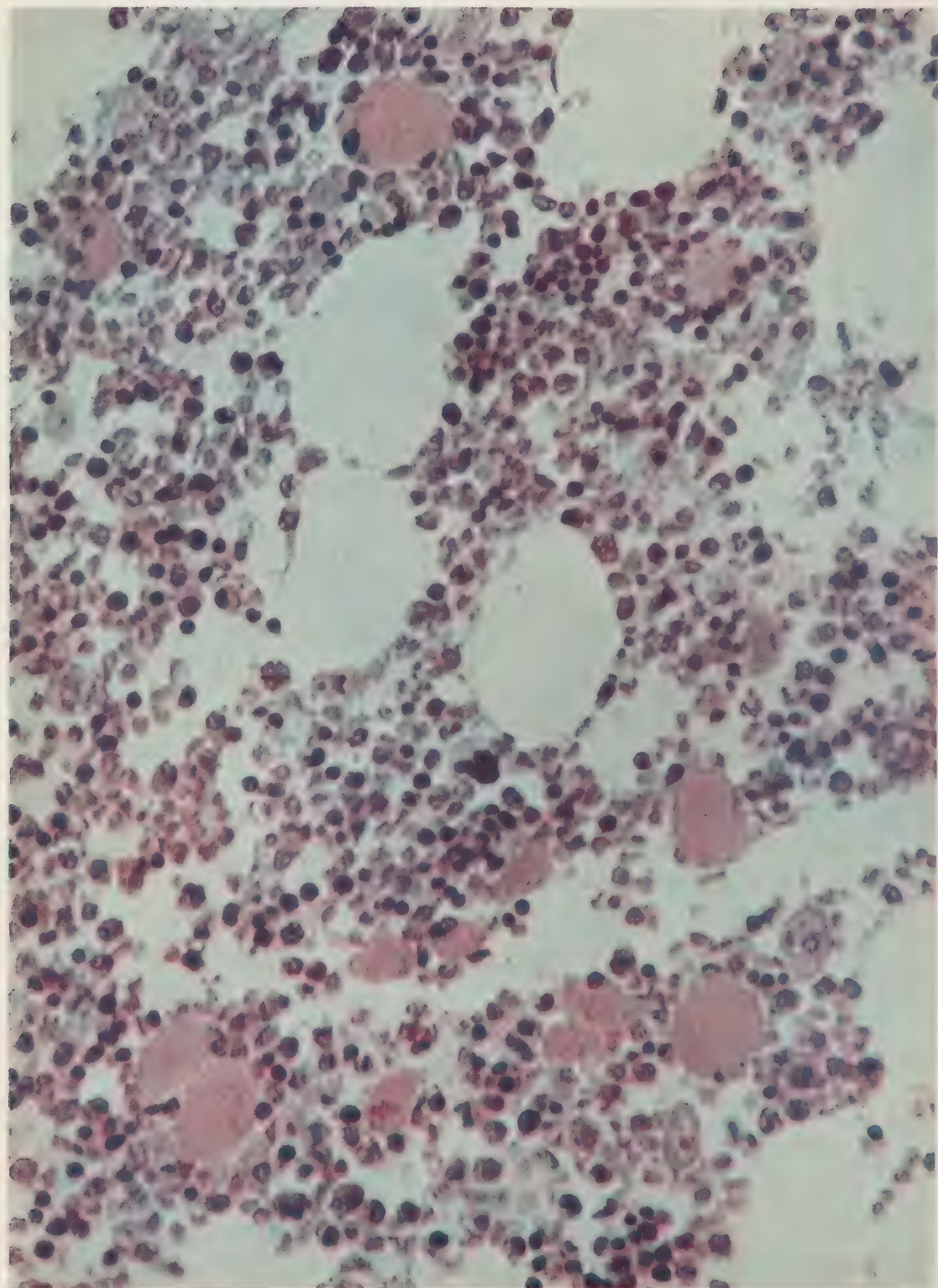


FIGURE 55. Duration of illness, 32 hours. There appears to be a distinct increase in the number of megakaryocytes in the marrow. Most have lost their nuclei; the few nuclei remaining are greatly shrunken. AIP Acc. 86617.

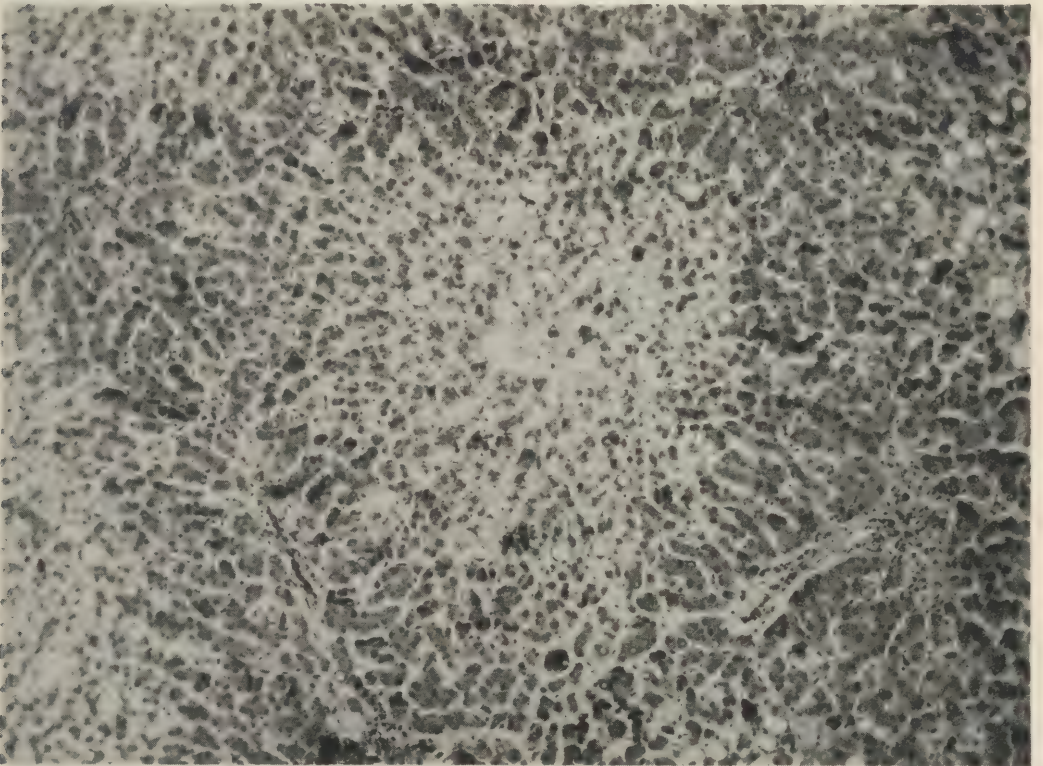
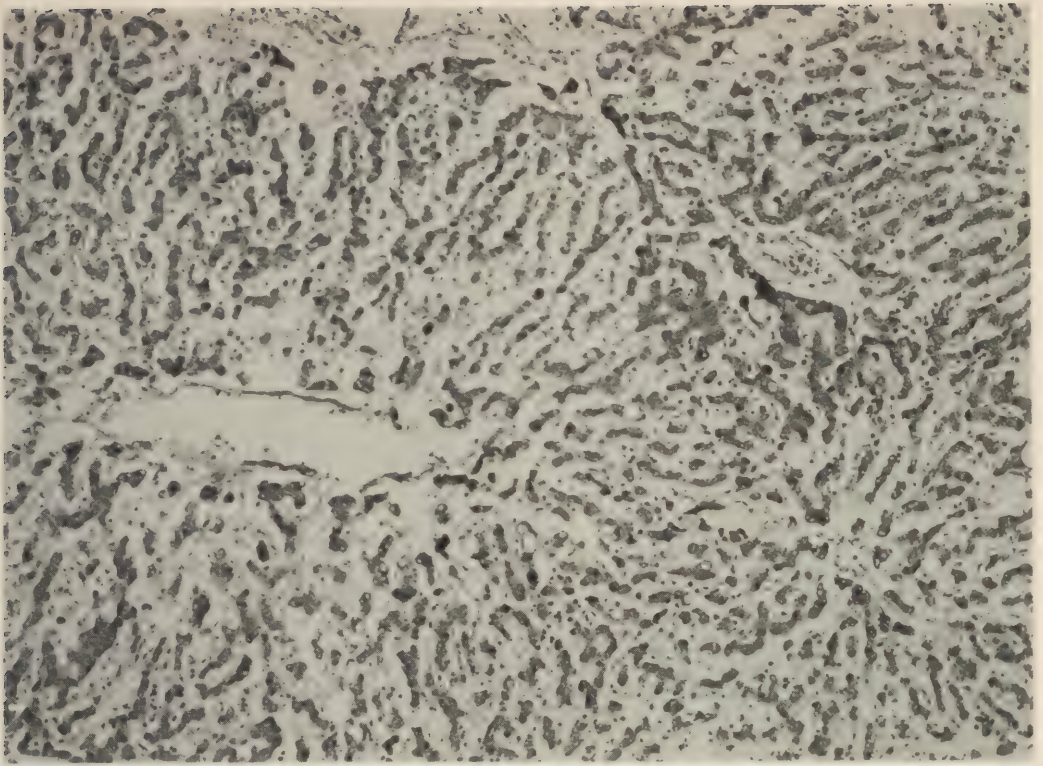


FIG. 47. Duration of illness, 6 hours. Owing to advanced perisinusoidal edema the liver cords are widely separated. A moderate dissociation of liver cords is visible. The sinusoids proper are dilated. The liver weighed 1750 gm. $\times 100$. AIP Acc. 98519.

FIG. 48. Duration of illness, 276 hours. Liver cells in the central portion of the lobules are extensively degenerated and there is considerable fatty change. Liver cords of the lobular periphery show a moderate degree of dissociation. The icterus index was 16 and clinically there was a suggestion of jaundice. The Prussian blue reaction for iron was negative. The liver weighed 2350 gm. $\times 110$. AIP Acc. 118078.

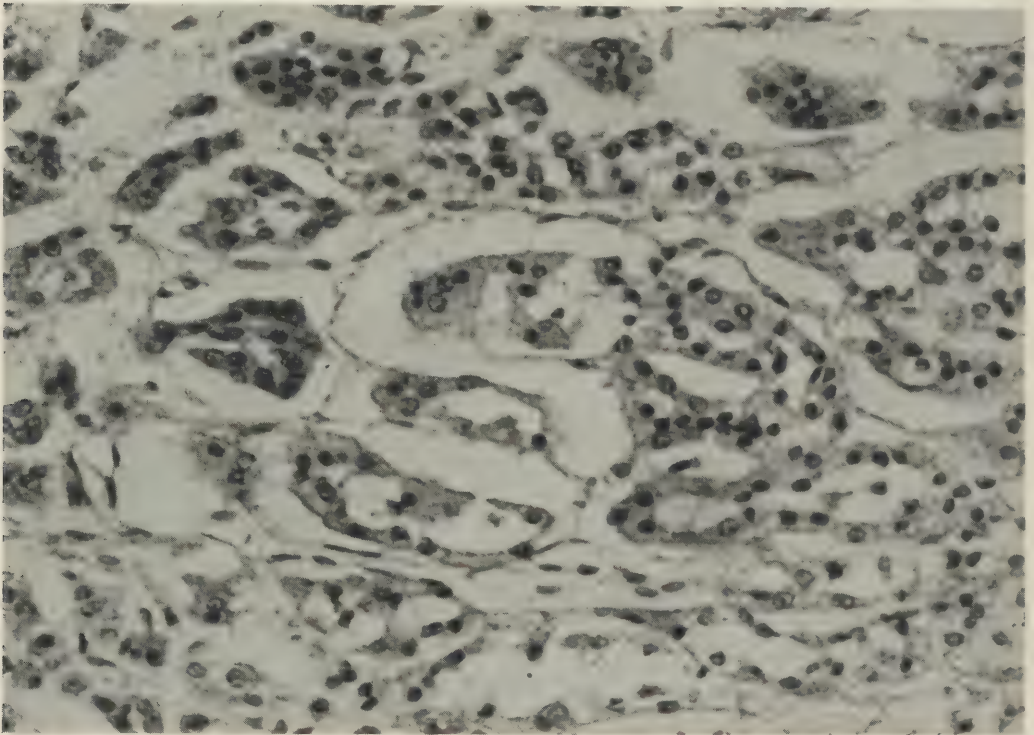
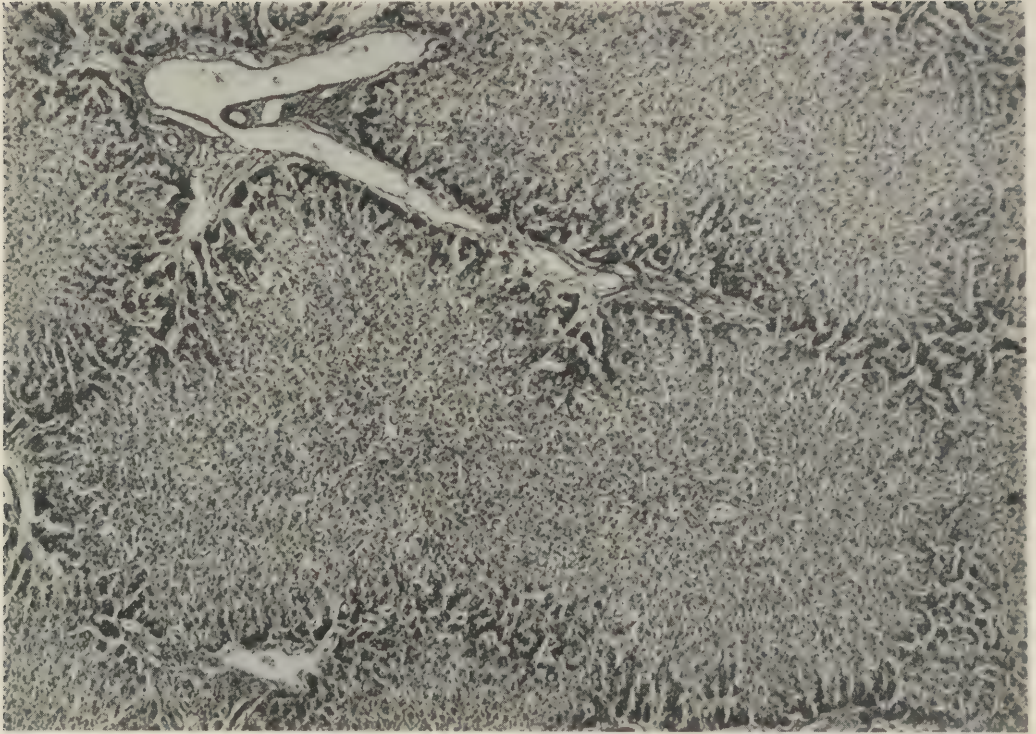


FIG. 49. Duration of illness, 96 hours. Autopsy was performed $1\frac{1}{2}$ hours after death. Necrosis of lobules is far advanced. No jaundice was observed. $\times 50$. AIP Acc. 95093.

FIG. 50. Duration of illness, 48 hours. The adrenal cortex is the seat of so-called tubular degeneration. Cells of the zona fasciculata, because of separation in the longitudinal axis of the columns, have taken on a tubular arrangement. A few of the cells seem to be undergoing disintegration. There is considerable perisinusoidal edema. $\times 350$. AIP Acc. 95888.

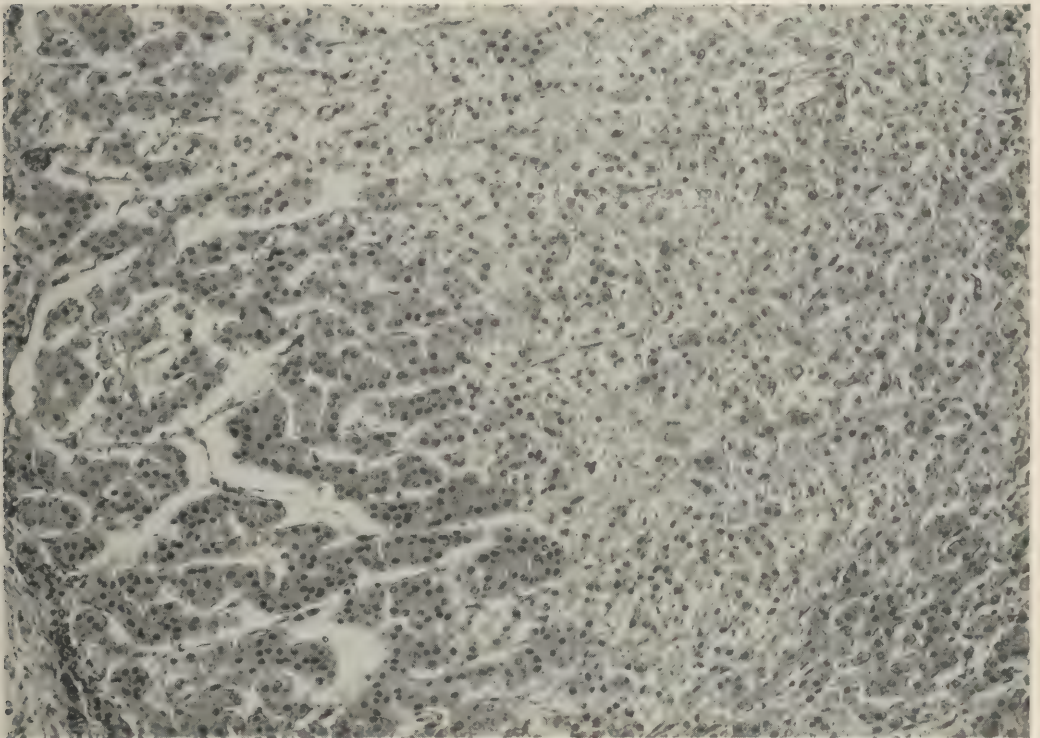
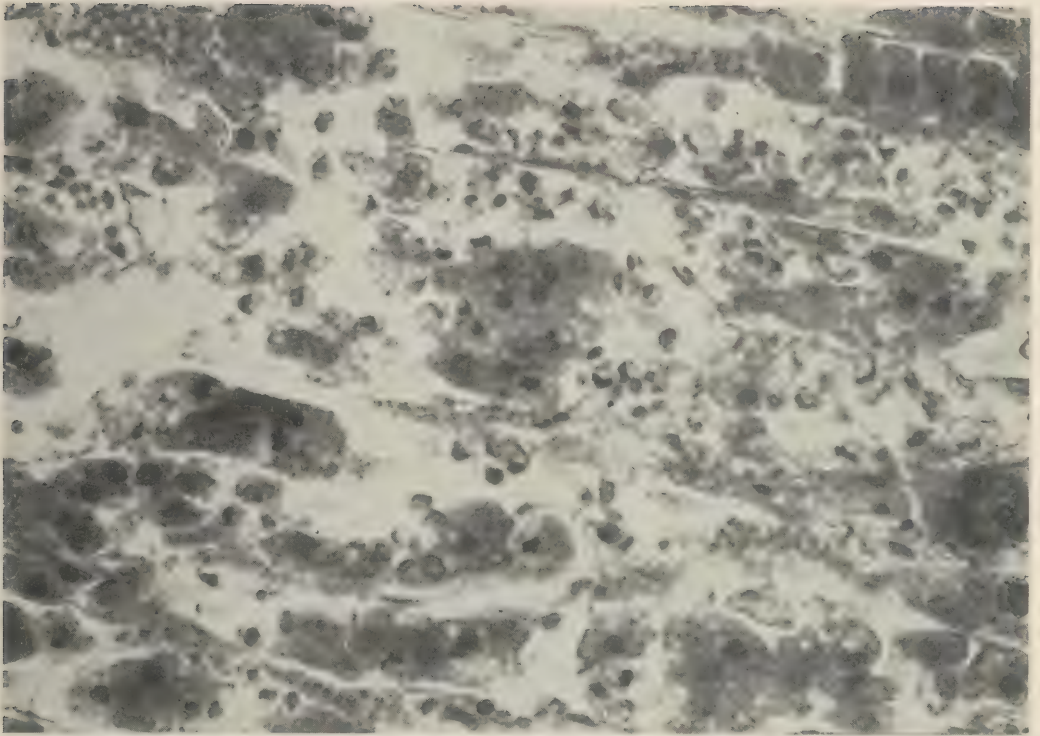


FIG. 51. Duration of illness, 35 hours. Numbers of necrotic cells of the mid-portion of the zona fasciculata are surrounded by smaller cells regarded as macrophages. The sinusoids are engorged. $\times 500$. AIP Acc. 97148.

FIG. 52. Duration of illness, 72 hours. Autopsy was performed $2\frac{1}{2}$ hours after death. A large area of the adrenal cortex displays early necrosis. The intact cells are deficient in lipoids. $\times 160$. AIP Acc. 96554.

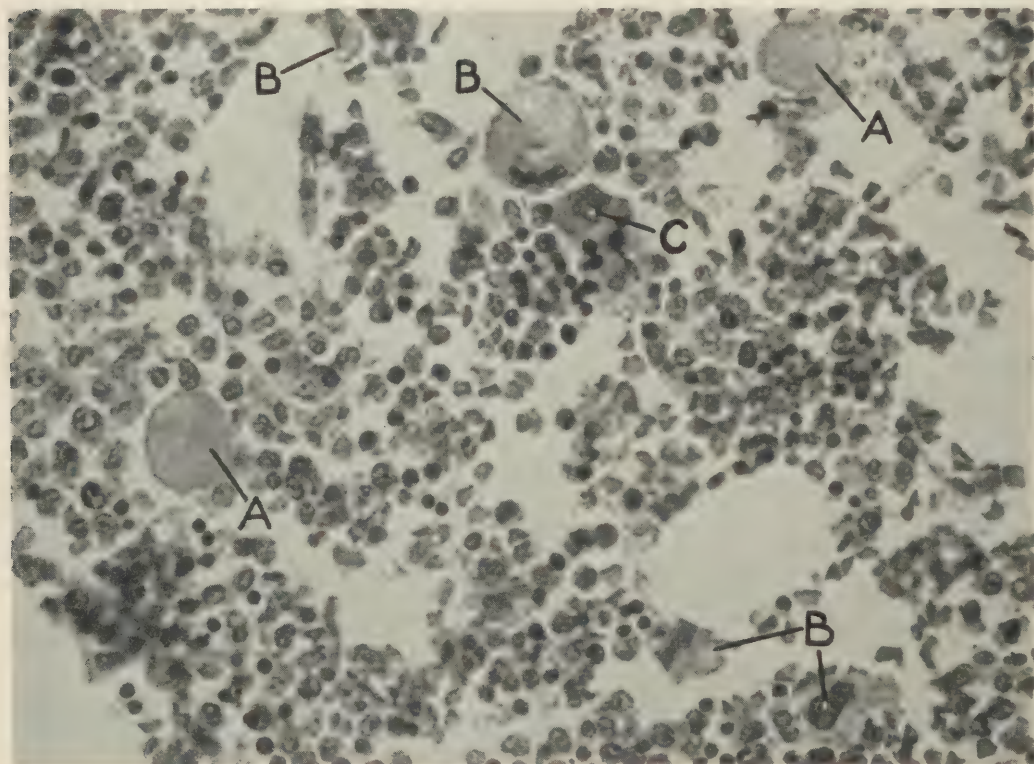
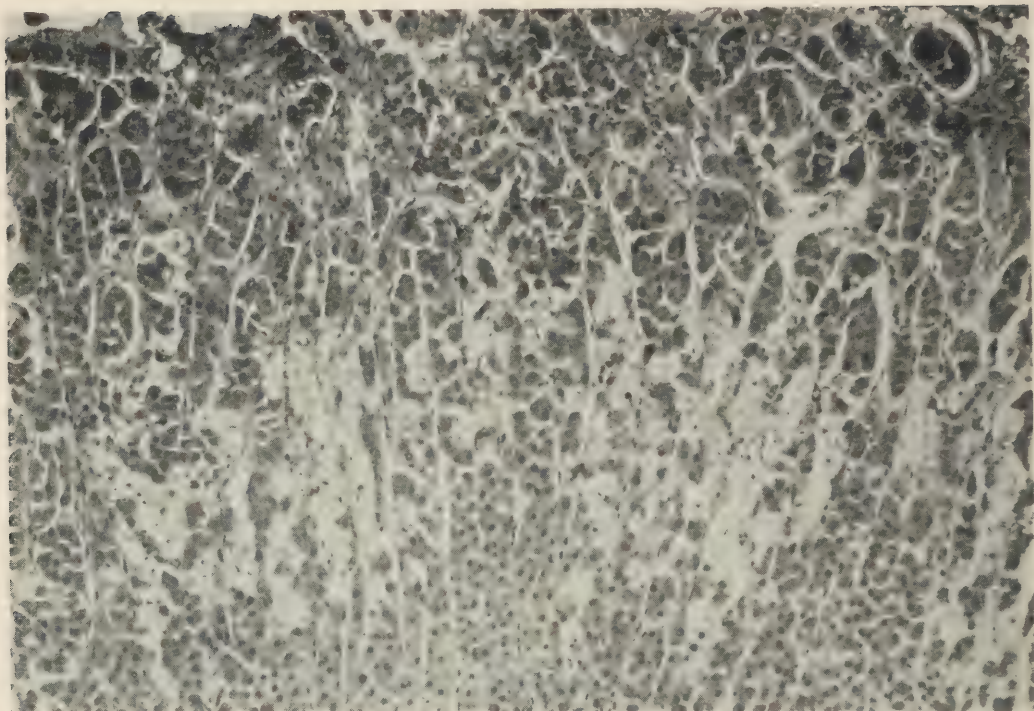


FIG. 53. Duration of illness, 130 hours. The adrenal cortex is depleted of lipoids and is the seat of focal necrosis. The cells in these foci have almost completely disappeared, leaving the empty stromal framework. $\times 130$. AIP Acc. 115309.

FIG. 54. Duration of illness, 6 hours. The bone marrow is greatly congested. The megakaryocytes show advanced degenerative changes; two of them (A) have lost their nuclei, while in four others (B) only remnants of the nuclei remain. One young megakaryocyte (C) is visible. $\times 650$. AIP Acc. 99445.

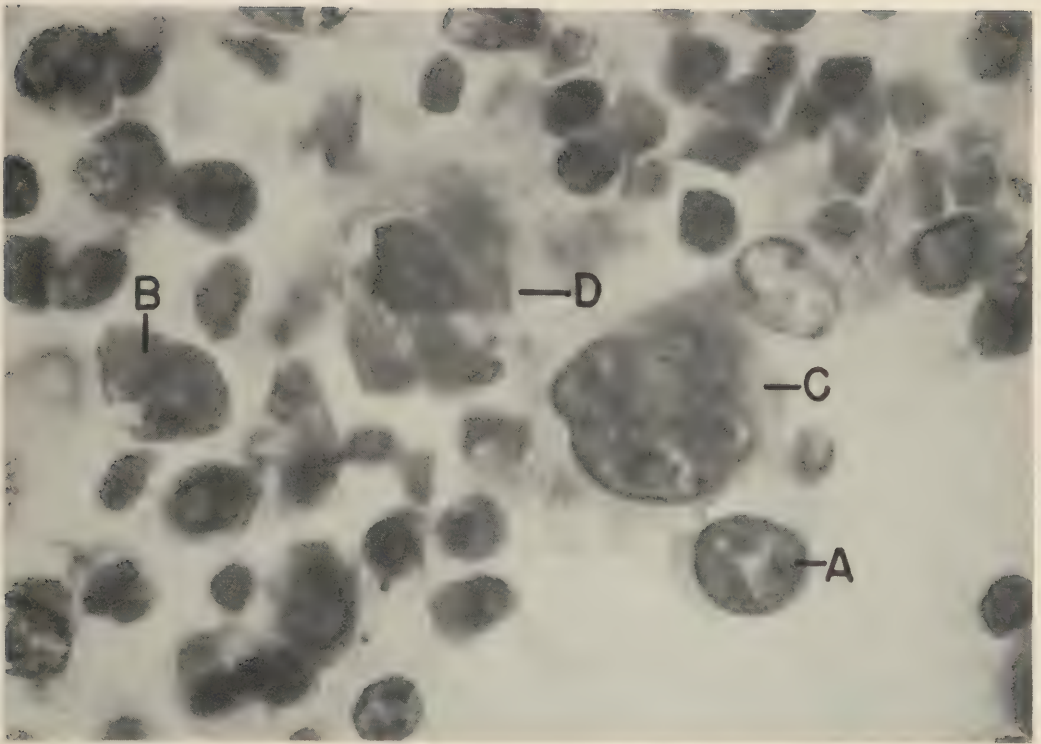


FIG. 56. Duration of illness, 26 hours. In this bone marrow section, four cells of the megakaryocytic series are present. The cell indicated by *A* is a megakaryoblast, by *C* a fully matured megakaryocyte, by *B* an intermediate developmental form, and by *D* a degenerating megakaryocyte. $\times 1670$. AIP Acc. 97555.

less than an hour to twelve days; in 30 per cent it was more than 24 hours.

Among the more frequent laboratory findings were the following: early-developing blood leukocytosis; normal hemoconcentration with a tendency to hydremia; a moderate rise in nonprotein nitrogen content of the blood and a lesser elevation of urea nitrogen, both apparent in the earlier stages of the disorder, and a decrease in CO_2 combining power. Too few figures were available to permit an assessment of the status of the blood chlorides. The changes appeared to be identical with those associated with shock. Platelets were consistently decreased in number early in the course of the disorder, and prothrombin and bleeding times were frequently increased later. The defect in blood coagulation was probably due to the thrombocytopenia rather than hypoprothrombinemia, as the platelets sometimes reached critical levels whereas prothrombin time did not. This was regarded as a con-

sequence of hyperthermia. Other laboratory findings consisted of elevated icterus index, and albumin, casts, and red blood cells in the urine in some cases of longer standing.

Pathologic changes in the central nervous system were most conspicuous, and consisted of 1) progressive degeneration of neurons and replacement by glia, especially in the cerebellum, cerebral cortex, and basal ganglia, but not in the hypothalamus or the rest of the brain stem, the severity of the changes corresponding to the length of survival after the occurrence of hyperthermia; 2) congestion, edema, and petechial hemorrhages, most commonly in the region of the third ventricle, the aqueduct, and the fourth ventricle, all of which were inconstant and regarded as terminal. In our opinion the cellular changes were caused by excessive heat, and the hemorrhages by shock. The changes in thoracic and abdominal viscera also may be divided into two categories: hemorrhages and parenchymal lesions. Hemor-

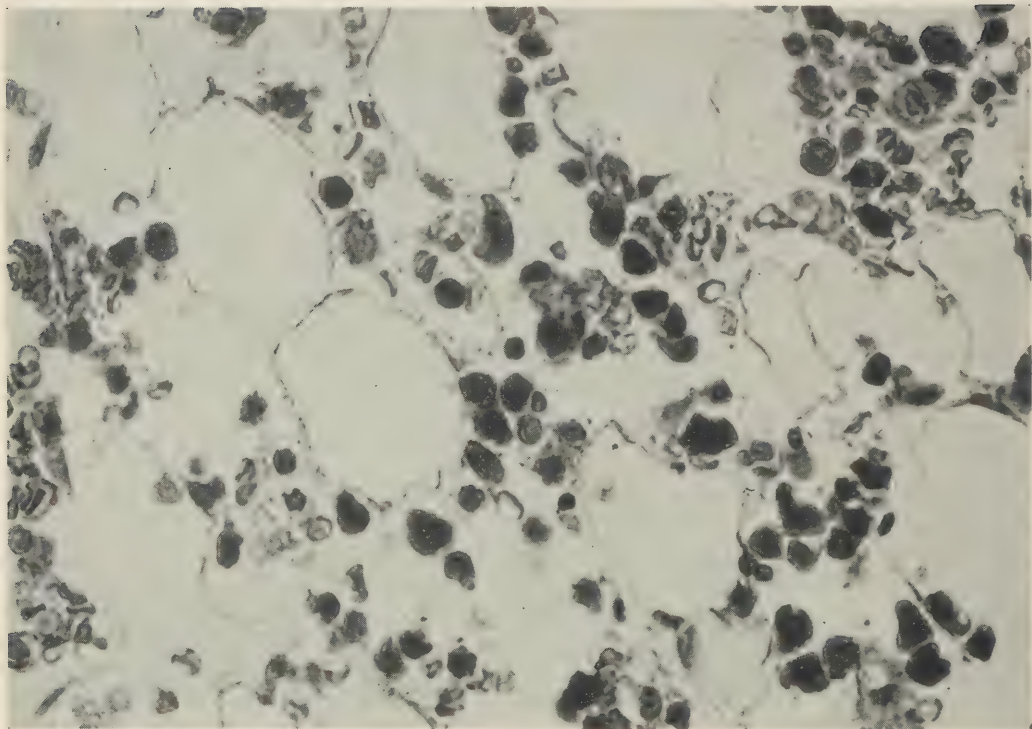


FIG. 57

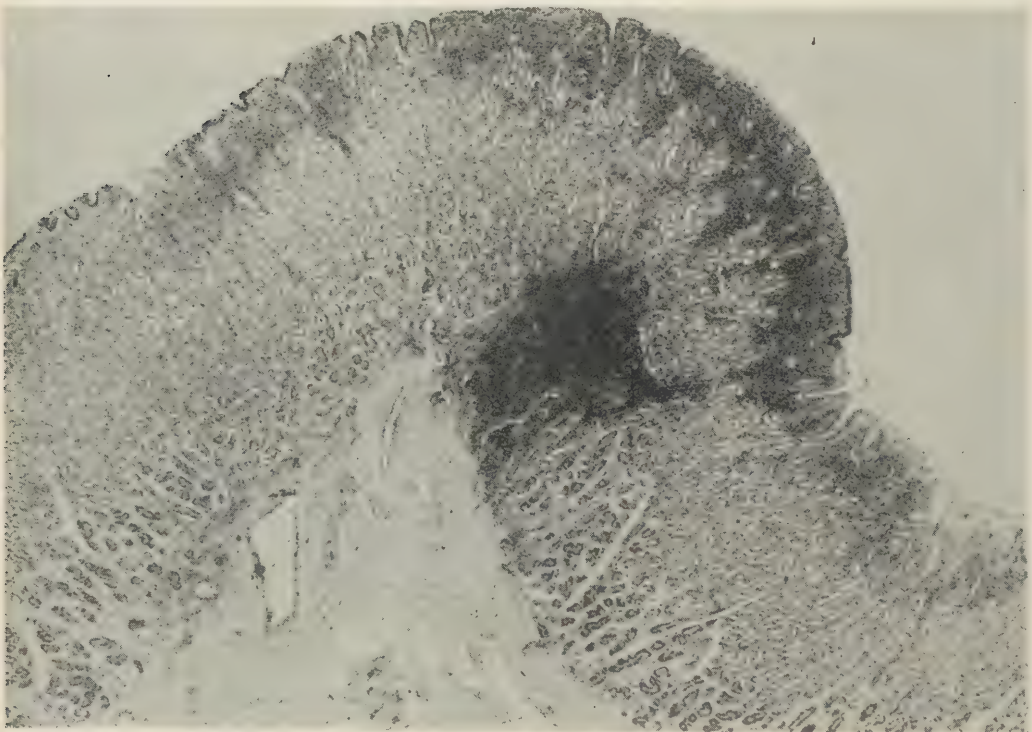


FIG. 58

rhages occurred in a wide variety of structures regardless of the duration of the illness, especially in the lungs, subepicardial and subendocardial tissues, and in the region of the bundle of His. Parenchymal lesions were predominant in cases in which survival was more than 24 hours, consisting, in order of their frequency, of degeneration and subsequent regeneration of megakaryocytes, necrosis of heart muscle, lobular pneumonia, lower nephron nephrosis, centrolobular necrosis of the liver, and degenerative changes in the adrenal cortex. In some cases there were varying combinations of these disorders.

The clinical, laboratory and pathologic findings indicate that two factors are operative in heat stroke: hyperthermia and shock. It would seem that increased body temperature imparts to the disorder a specific character, affecting tissues of the organism to varying degrees. Our data yield no definite information on the mechanism underlying the temperature disturbance but the hypothesis is advanced that heat irreparably impairs the thermostatic function of the hypothalamus and that as a consequence the autonomic nervous system is no longer capable of reestablishing sweating or adequate peripheral circulation. Where anoxic anoxia or other conditions combined with severe shock leads to the same sequence of clinical events it is believed that the same mechanism is at fault. But although shock undoubtedly plays a significant role in the course of heat stroke, including an augmentation of body temperature owing to peripheral vasoconstriction, it is regarded as a secondary manifestation and therefore non-specific and unessential to the fundamental pathogenesis of the disorder.

REFERENCES

- ¹ Adolph, E. F.: Physiological fitness for the desert, *Federation Proc.* 2:158-165, 1943.
- ² Adolph, E. F., and Fulton, W. B.: The effects of exposure to high temperatures upon the circulation in man, *Am. J. Physiol.* 67:573-588, 1924.
- ³ Alpers, B. J.: Hyperthermia due to lesions in the hypothalamus, *Arch. Neurol. & Psychiat.* 35:30-42, 1936.
- ⁴ Antheaume, A., and Mignot, R.: Insolation et paralysie générale. Quelques particularités cliniques, *Encéphale* 3:493-591, 1908.
- ⁵ Aron, H.: Investigation on the action of the tropical sun on men and animals, *Philippine J. Sc., B., Med. Sc.* 6:101-132, 1911.
- ⁶ Bazett, H. C., Sunderman, F. W., Doupe, J., and Scott, J. C.: Climatic effects on volume and composition of blood in man, *Am. J. Physiol.* 129:69-83, 1940.
- ⁷ Bean, W. B., and Eichna, L. W.: Performance in relation to environmental temperature. Reactions of normal young men to simulated desert environment, *Federation Proc.* 2:144-158, 1943.
- ⁸ Beaton, L. E., and Herrmann, J. D.: Hyperthermia following injury of the preoptic region, *Arch. Neurol. & Psychiat.* 53:150-151, 1945.
- ⁹ Blalock, A., and Price, P. B.: Panel discussions; traumatic shock—early signs, prevention and treatment, *Bull. Am. Coll. Surgeons* 27:102-105, 1942.
- ¹⁰ Blum, H. F.: The physiological effects of sunlight on man, *Physiol. Rev.* 25:483-530, 1945.
- ¹¹ Blum, H. F.: The solar heat load; its relationship to total heat load and its relative importance in the design of clothing, *J. Clin. Investigation* 24:712-721, 1945.
- ¹² Castellani, A.: *Climate and Acclimatization*, ed. 2, London, Bale & Curnow, 1938.
- ¹³ Chakravarti, D. N., and Tyagi, N.: Studies in effects of heat, *Ind. J. Med. Res.* 25:791-827, 1938.
- ¹⁴ Cournand, A., Riley, R. L., Bradley, S. E., Breed, E. S., Noble, R. P., Lauson, H. D., Gregersen, M. I., and Richards, D. W.: Studies of the circulation in clinical shock, *Surgery* 13:964-995, 1943.
- ¹⁵ Cullen, S. C., Weir, E. F., and Cook, E.: The rationale of oxygen therapy during fever therapy, *Arch. Phys. Therap.* 23:529-535, 1942.
- ¹⁶ Davison, C.: Disturbances of temperature regulation in man, *A. Research Nerv. & Ment. Dis., Proc.* 20:774-823, 1940.
- ¹⁷ Fleck, U., and Hükel, R.: Zur Klinik und Pathologie des Hitzschlages, *Deutsche Ztschr. f. Nervenhe.* 117:113-137, 1931.
- ¹⁸ Freeman, W., and Dumoff, E.: Cerebellar syndrome following heat stroke, *Arch. Neurol. & Psychiat.* 51:67-72, 1944.
- ¹⁹ Gauss, H., and Meyer, K. A.: Heat stroke: re-

FIG. 57. Duration of illness, 74 hours. Between fat cells of the marrow interstices there is marked depletion of hematopoietic cells of all categories. The section was taken from a rib, the marrow of which should be nearly 50 per cent cellular in this age group. $\times 650$. AIP Acc. 98544.

FIG. 58. Duration of illness, 13½ hours. The mucosa of the stomach is the seat of deep punctate and superficial diffuse hemorrhage. The submucosa is congested and edematous. $\times 30$. AIP Acc. 101019.

port of one hundred and fifty-eight cases from Cook County Hospital, Chicago, *Am. J. M. Sc.* 154:554-564, 1917.

²⁰ Gemmill, C. L.: *Physiology in Aviation*, Springfield, Illinois, Charles C Thomas, 1943.

²¹ Gildea, E. F., and Cobb, S.: The effects of anemia on the cerebral cortex of the cat, *Arch. Neurol. & Psychiat.* 23:876-903, 1930.

²² Goebel, A. J. L.: *Ueber die Nachkrankheiten des Hitzschlages*, Berlin, O. Franke, 1905.

²³ Hall, W. W., and Wakefield, F. G.: A study of experimental heatstroke, *J. A. M. A.* 89:177-182, 1927.

²⁴ Hartman, F. W., and Major, R. C.: Pathological changes resulting from accurately controlled artificial fever, *Am. J. Clin. Path.* 5:392-410, 1935.

²⁵ Heilman, M. W., and Montgomery, E. S.: Heat disease, *J. Indust. Hyg. & Toxicol.* 18:651-667, 1936.

²⁶ Horvath, S. M., Dill, D. B., and Corwin, W.: Effects on man of severe oxygen lack, *Am. J. Physiol.* 138:659-668, 1943.

²⁷ Hyndman, O. R., and Wolkin, J.: The automatic mechanism of heat conservation and dissipation, *Am. Heart J.* 289-304, 1941.

²⁸ Keller, A. D.: Separation in the brain stem of the mechanisms of heat loss from those of heat production, *J. Neurophysiol.* 1:543-557, 1938.

²⁹ Kopp, I.: Metabolic rates in therapeutic fever, *Am. J. M. Sc.* 190:491-501, 1935.

³⁰ Kopp, I., and Solomon, H. C.: Shock syndrome in therapeutic hyperpyrexia, *Arch. Int. Med.* 60:597-622, 1937.

³¹ Ladell, W. S. S., Waterlow, J. C., and Hudson, M. F.: Desert climate. Physiological and clinical observations, *Lancet* 2:491-497, 527-531, 1944.

³² Manson, P.: *Manson's Tropical Diseases. A Manual of the Diseases of Warm Climates*. Edited by P. H. Manson-Bahr. Baltimore, Williams & Wilkins, 1940.

³³ Marsh, F.: The etiology of heat stroke and sun traumatism, *Tr. Roy. Soc. Trop. Med. & Hyg.* 24:257-288, 1930.

³⁴ McKendrick, J. G.: A case of meningo-cerebritis, caused probably by exposure to the sun, *Edinburgh M. J.* 14:517-522, 1868.

³⁵ McKenzie, P., and LeCount, E. R.: Heat stroke, *J. A. M. A.* 71:260-263, 1918.

³⁶ Messiter, A. F.: A case of insolation accompanied by hemiplegia, *Lancet* 1:1741-1742, 1897.

³⁷ Moon, V. H.: The vascular and cellular dynamics of shock, *Am. J. M. Sc.* 203:1-18, 1942.

³⁸ Moon, V. H.: *Shock. Its Dynamics, Occurrence and Management*. Philadelphia, Lea & Febiger, 1942.

³⁹ Morgan, L. O.: Cell changes in some of the hypothalamic nuclei in experimental fever, *J. Neurophysiol.* 1:281-285, 1938.

⁴⁰ Morgan, L. O., and Vonderahe, A. R.: The

hypothalamic nuclei in heat stroke, *Arch. Neurol. & Psychiat.* 42:83-91, 1939.

⁴¹ Omorokow, L.: Ueber den Einfluss hoher Temperaturen auf das Zentralnervensystem des Kaninchens, *Histol. u. Histopath. Arbeiten, Nissl-Alzheimer* 6:1-32, 1913.

⁴² Ranson, S. W.: Regulation of body temperature, *A. Research Nerv. & Ment. Dis., Proc.* 20:342-399, 1940.

⁴³ Reid, W. D.: Pneumonia not a rare complication of heat prostration, *Boston M. & S. J.* 167:217-219, 1912.

⁴⁴ Rich, A. R.: Peculiar type of adrenal cortical damage associated with acute infections, and its possible relation to circulatory collapse, *Bull. Johns Hopkins Hosp.* 74:1-15, 1944.

⁴⁵ Richards, D. W., Jr.: The circulation in traumatic shock in man, *Bull. N. Y. Acad. Med.* 20:363-393, 1944.

⁴⁶ Rosenbaum, L.: Significance of salt (NaCl) in torrid temperatures, *MILITARY SURGEON* 98:43-47, 1946.

⁴⁷ Rosenblath: Zur Pathologie der Encephalitis acuta, *Deutsche Ztschr. f. Nervenhe.* 50:342-405, 1914.

⁴⁸ Schickele, E.: Environment in fatal heat stroke. An analysis of 157 cases occurring in the Armed Forces in the United States during World War II, *MILITARY SURGEON*, Dec. 1946.

⁴⁹ Schwab, W.: Ueber Hirnveränderungen bei Sonnenstich, *Schweiz. med. Wchnschr.* 55:33-38, 1925.

⁵⁰ Schwartz, P.: Die Arten der Schlaganfälle des Gehirns und ihre Entstehung, Berlin, J. Springer, 1930.

⁵¹ Shepherd, H. M. D.: Effects of heat in Iraq, *J. Roy. Army Med. Corps* 84:1-8, 1945.

⁵² Steinhausen, F. A.: *Nervensystem und Insolation*, Berlin, A. Hirschwald, 1910.

⁵³ Stern, K.: Über Kreislaufstörungen im Gehirn bei Wanderrissen in extracerebralen Arterien, *Ztschr. f. d. ges. Neurol. u. Psychiat.* 148:55-82, 1933.

⁵⁴ Stewart, R. M.: On the occurrence of a cerebellar syndrome following heat stroke, *Rev. Neurol. & Psychiat.* 16:78-93, 1918.

⁵⁵ Tavel, F. von: Die Auswirkungen des Sauerstoffmangels auf den menschlichen Organismus bei kurzfristigem Aufenthalt in grosser Höhe. Ein Beitrag zur Frage der Leistungsfähigkeit im Höhenflug, *Helv. Physiol. Pharmacol. Acta (suppl. 1)*, pp. 1-128, 1943.

⁵⁶ Titrud, L. D., and Haymaker, W.: Cerebral anoxia from high altitude asphyxiation, *Arch. Neurol. & Psychiat.* (in Press).

⁵⁷ van Bogaert, L., Dallemagne, M. J., and Wégria, R.: Recherches sur le besoin d'oxygène chronique et aigü chez *Macacus rhesus*. Absence de lésions expérimentales des centres nerveux après intoxication

par l'oxyde de carbone, le nitrite de soude et l'appauvrissement de l'air en oxygène, *Arch. internat. de Med. expér.* 13:335-378, 1938.

⁵⁸ Wakefield, E. G., and Hall, W. W.: Heat injuries. A preparatory study for experimental heat-stroke, *J.A.M.A.* 89:92-95, 1927.

⁵⁹ Wallace, A. W.: Heat exhaustion, *MILITARY SURGEON* 93:140-146, 1943.

⁶⁰ Wallace, J., and Bushby, S. R. M.: Hazards of hypertherm treatment, *Lancet* 2:459-464, 1944.

⁶¹ Ward, R. L., and Olson, O. C.: Report of a case of severe anoxic anoxia with recovery, *J. Aviation Med.* 14:360-365, 1943.

⁶² Weiner, J. S.: Experimental study of heat collapse, *J. Indust. Hyg. & Toxicol.* 20:389-400, 1938.

⁶³ Weisenburg, T. H.: Nervous symptoms following sunstroke, *J.A.M.A.* 58:2015-2017, 1912.

⁶⁴ Wilcocks, C.: Heat stroke and allied conditions, *Practitioner* 147:463-468, 1941.

⁶⁵ Willcox, W. H.: The nature, prevention, and

treatment of heat hyperpyrexia; the clinical aspect, *Brit. M. J.* 1:392-397, 1920.

⁶⁶ Wilson, G.: The cardiopathology of heat-stroke, *J.A.M.A.* 114:557-558, 1940.

⁶⁷ Wilson, S. J., and Doan, C. A.: The pathogenesis of hemorrhage in artificially induced fever, *Ann. Int. Med.* 13:1214-1229, 1939.

⁶⁸ Windle, W. F., and Becker, R. F., and Weil, A.: Alterations in brain structure after asphyxiation at birth, *J. Neuropath. & Exper. Neurol.* 3:224-238, 1944.

⁶⁹ Wright, R. D., and Devine, J.: Body temperatures in shock, *M. J. Australia* 1:21-27, 1944.

⁷⁰ Wright, D. O., Reppert, L. B., and Cuttino, J. T.: The purpuric manifestations of heat stroke. A report of prothrombin and platelet studies in twelve cases. (in preparation).

⁷¹ Zimmerman, H. M.: Temperature disturbances and the hypothalamus, *A. Research Nerv. & Ment. Dis., Proc.* 20:824-840, 1940.

FATAL PULMONARY EMBOLISM IN 100 BATTLE CASUALTIES*

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(With two illustrations)

NOT long after D day in Normandy an apparent disproportionate number of deaths from pulmonary embolism following battle wounds aroused interest at the laboratory[¶] where the majority of these cases were first reviewed. Because pulmonary embolism seemed a more frequent cause of death than accumulated experience would have suggested, a survey was made of 1065 autopsies on cases in which battle wounds had recently been sustained. It was found that in 66, or 6.19 per cent of these, death was due to pulmonary embolism. These cases, augmented by 34 others available for study at the Army Institute of Pathology, form the basis for this paper.

It is necessary to have it clearly understood at the outset that the term "fatal pulmonary embolism" has been employed advisedly in this report which is based on the analysis of autopsy protocols. This usage is consistent with the recent interpretation of Murnaghan, McGinn and White¹ (1943), who write, "It is emphasized that 'pulmonary embolism' and 'acute cor pulmonale' are not synonymous terms." Acute cor pulmonale was described originally by McGinn and White in 1935.²

The first report of pulmonary embolism was made by Virchow³ in 1846. Trauma, childbirth, and disease were the predisposing conditions before the days of modern surgery. The literature has recently been thoroughly reviewed by McCartney,⁴ who also presented the results of an analysis of 25,771 necropsies in which the incidence of fatal pulmonary embolism was 2.6 per cent. In an exhaustive study

of fatal pulmonary embolism following trauma published in 1935, McCartney⁵ reported an incidence of 4.0 per cent in post-traumatic cases in contrast to 2.6 per cent in cases without trauma. He explained the disparity in sex incidence in this series (2.5 per cent in males and 8.6 per cent in females) on the grounds of the greater prevalence of pre-existing varicosities in women.

The largest series of cases of post-traumatic fatal pulmonary embolism previously reported are those of McCartney⁴ and Vance.⁶ Their observations present certain basic differences from, and few analogies with, ours. In McCartney's series, 33 of 61 were in men, only 3 of whom were under 40 years of age. In Vance's series, 23 of the 60 were males; 14 were less than 50, and only 4 less than 40 years of age. Our series, drawn from combat troops, was comprised entirely of men, 1 of whom was over 40.

A possible virtue of an analysis of battle casualties is the absence of such usually plaguing variables as age and previous or intercurrent disease since all had presumably been physically fit soldiers. Sex and color as influencing factors are eliminated, because all of these soldiers happened to be white. Study of the relationship of trauma to thrombosis and embolism is also possible, since all emboli followed injury.

The preliminary observation that pulmonary embolism was more frequent when wounds were in the region of the leg and hip was borne out by subsequent study. The percentage of leg and hip wounds in the entire battle casualty group was 29 per cent, whereas it was 53 per cent (calculation based upon site of single wounds and fractures) in cases of fatal pulmonary embolism. Figures from World War I,⁷ indicate a high mortality following wounds of the lower extremities. Of all the fatalities resulting from battle wounds

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among the American troops in Europe from 1917 to 1919, 42.2 per cent followed injury to the lower extremities; of course gas gangrene was responsible for a majority of these.

An analysis of the material in this series has been attempted for the purpose of determining the role of certain factors in fatal pulmonary embolism. These include: (1) age; (2) type of case; (3) distribution of wounds; (4) site of fractures; (5) interval between injury and death; (6) associated factors possibly precipitating attacks; (7) symptoms; (8) duration of pulmonary embolism; (9) incidence and location of pulmonary infarcts; (10) site of massive emboli; (11) alteration of the heart; (12) location of phlebothrombosis, and (13) relationship of anatomic considerations to thrombosis and embolism.

Age. The limits of variation in age of 89 cases in which it was recorded are 17 and 41 years, and, if the 6 prisoners of war are excluded, the range is from 19 to 38 years. The mean calculated from either set of figures is 26 years (Table I). All except 7 per cent of these men were in their twenties or thirties and were without known physical disabilities at the time they were wounded, making this series unlike others reported, since it comprised young healthy men.

Type of Case. To give a proper perspective on the problem the cases may be classified from the point of view of the clinician. There are three major groups of patients for whom immobilization is a necessary concomitant of treatment; those (1) in casts, (2) with post-operative laparotomies, and (3) with penetrating wounds of the chest.

The significance of immobilization and lack of exercise as underlying factors has been clearly indicated by the clinical study of Potts and Smith.⁸ Although many protocols omit specific designation of treatment, in general the data from our series support their findings. At least one-fourth of the patients with fatal pulmonary embolism had been immobilized by casts, usually on the lower extremities, body, or both. Two had casts on the arms. Traction was being applied for at least two fractures of the leg at the time of death.

Laparotomy had been performed in 24 cases. In 23 a serious consideration was penetrating wounds of the chest.

Attention is focused again on the role of trauma of the lower extremities by the 14 deaths from pulmonary embolism following amputation. Shock was prominent early in most cases, particularly in those of traumatic amputation. Other possible predisposing factors

TABLE I
DECADE IN WHICH FATAL PULMONARY
EMBOLISM OCCURRED

Decade	2nd	3rd	4th	5th
Number of Deaths	6	54	28	1

were extensive local operative procedures, including those on blood vessels. Four patients were in serious condition because of penetrating wounds of the head, and 3 because of damage to the spinal cord.

In 9 of the cases it was stated that the patient had been in severe shock. Transfusions are known to have been given in 37 per cent, but there is a lack of recorded information in regard to blood and plasma, which almost routinely have been given such wounded patients.

Overlapping conditions placed 14 cases in more than one category. In only 3 was there no evident predisposing factor for thrombosis such as venous stasis or damage to tissue or blood vessels.

It is significant that 91 of the wounds were either penetrating or perforating. The type of wound and extent of damage to soft tissues and bones are largely dependent on the nature of the missiles producing them. Data on the missiles were given in 75 of the protocols and in general they could be grouped as shell fragments or bullets. In 58 cases there were shell fragments; high explosive from such sources as 88 mm. guns, cannons, German bazookas, aerial bombs, and also shrapnel and mines. Bullet wounds were recorded in 14 cases, 8 from machine gun and 6 from rifle; 3 were classified simply as gunshot wounds.

Distribution of Wounds. Although evalua-

tion of the relationship of local trauma to thrombosis and embolism is highly desirable, the multiplicity of wounds in individual cases complicated such an analysis (Table II). Eighty-two of 211 wounds in the 100 cases were in the lower extremities, 13 in the buttock, 8 in the pelvis, and 3 in the hip. The upper extremities were involved in 20 instances. Chest wounds, most of which were penetrating, were present in 28, while the

TABLE II
DISTRIBUTION OF WOUNDS AND FRACTURES

Site of Wounds	Number	Site of Fractures
1. Head and Neck	13	4
Skull, penetrating wounds	(4)	(4)
2. Chest	28	12
3. Abdomen	20	
4. Back (including all vertebrae)	24	13
5. Pelvis, Buttock and Hip	24	8
Pelvis	(8)	(8)
Buttock and Hip	(16)	—
6. Lower Extremity	82	37
Right	(44)	(23)
Left	(37)	(14)
Thigh	(51)	(24)
Leg and Foot	(31)	(13)
7. Upper Extremity	20	8
	211	82

abdomen was the site of 20, and the back of 24. There were 8 wounds of the head and 5 of the neck.

A single area only was involved in 50 cases. In this group there is an opportunity for correlation of wounds with vascular lesions; however, the relatively small number of cases limits the significance of such a correlation. Wounds of the lower extremities were observed in one-half (26 cases); penetrating wounds of the chest in 7; wounds of the abdomen in 3, and of the pelvic region in 4.

Site of Fractures. Twelve deaths following fractures have been reported by Lister⁹ in a series of 281 cases of fatal pulmonary embolism; 9 followed fractures of the femur, giving an incidence of 11 per cent in 80 cases

of fracture in this region. Pulmonary embolism occurred subsequent to 22.2 per cent of the 157 fractures in the lower extremities in McCartney's⁵ post-traumatic cases. He observed that pulmonary embolism was rare after fractures in other locations. Age was a contributing factor in his cases. The prolonged rest in bed and strict immobilization attendant on treatment of fractures of the lower extremities tend to promote stasis which is of primary importance in the production of phlebothrombosis.

In our series there were fractures in 65 cases, some of them multiple since there were 81 in all. There were 37 fractures of the lower extremity, preponderantly of the thigh (24). Twenty-three of the fractures of the lower extremity were on the right side, in contrast to 14 on the left. In 55 there was a single site of fracture, so that in this group a correlation of injury with local vascular thrombosis might be attempted.

It is to be expected that in cases of fractured vertebrae (13), pelvis (8), and skull (4) venous stasis might have developed or vascular damage been sustained at the time of injury.

With the penetrating wounds of the chest, the fractures were of the ribs, scapulae, and vertebrae. Broken ribs may seem trivial unless one remembers that among the most grave are cases in which the missile passed through the thoracic cage in its course to deeper structures.

Interval from Injury until Death. The time interval from injury until death was 2 to 91 days; the mean was 18 and the average 20.7 days, both of which fall in the third week (Table III). The length of these intervals was the only clue to the time required for thrombus formation in 90 per cent of cases in which there was no evidence of embolism before the fatal attack. It may appear dubious to suggest stasis as the cause of phlebothrombosis in the short periods (e.g. 3 days) noted in 3 cases. Certain fatalities incident to this war, however, emphasize the lethal effects of stasis. A number of ambulatory but elderly persons have been victims of fatal pulmonary embolism, the result of stasis attributed to

pressure on the backs of their legs from wooden crossbars in their deck chairs, while in air raid shelters for relatively long intervals.¹⁰

Associated Factors, Possibly Precipitating Attacks. In connection with the attacks in about 30 per cent of cases in our series, there were incidents which may be interpreted as associated, or possibly precipitating, factors. Some of these appear trivial and may be coincidental as they constitute parts of the daily routine of hospitalization. They are presented as they were noted by the attending Medical

Officer. apparently well on the road to recovery, was building a fire; one was eating, and another had just finished a meal.

There were still other variations of the incidents which immediately preceded the fatal pulmonary embolism. One soldier had had a massage because of a cramp in his leg; another with pneumonia had been coughing and vomiting; a third had received a transfusion.

Symptoms. Clinical evidence of pulmonary embolism indicated by the symptomatology has been analyzed in the 78 cases in which

TABLE III
TIME OF DEATH IN RELATION TO DATE OF INJURY

Time in Weeks after Injury	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	11th	12th	13th
Number of cases	11	26	26	17	10	2	2	0	0	1	0	2	1

Officer.

Bowel movements were apparently related to 6 of the episodes; in 4, the fatal embolism occurred while the patient was on the bed pan, in 2, the patients had just returned from the latrine. One fatality took place after bladder irrigation.

Manipulation of a cast had been carried out in 6 cases a few minutes or hours before the accident. The attack took place after the cast had been changed in 4 instances; after it was cut in 1, and while it was being cut in another.

Passive activity was associated with fatal pulmonary embolism in 4 instances. One patient was being lifted; another fell out of bed; a third had just been transferred by ambulance from one hospital to another; and a fourth had been moved from a private room to a ward. In 3 cases the patient had returned from the operating room a few minutes or hours before he died of pulmonary embolism, but it was not possible to determine whether local manipulation or passive activity was the precipitating factor.

Exertion was associated with the attack in 4 cases. Two patients were out of bed, one was up in a wheel-chair, while a third, ap-

the history was detailed. Dyspnea dominated the picture, being present in about three-fourths of the cases. Although pain was a symptom at some time in approximately two-thirds, pain in the chest was observed in only one-third (33) during the terminal attack. Pain in the abdomen or leg was a conspicuous feature in approximately 10 per cent during the fatal episode. Abdominal pain was observed in 12 cases; in 5 it occurred in the absence of pain in the chest; in 11 without pain in the legs. In 5 cases the abdominal pain preceded the terminal attack, and in 3 it recurred during the fatal episode. The significance of abdominal pain has been discussed by Middleton¹¹ who interpreted it as based upon the vagus reflex from the pulmonary artery to the gastro-intestinal tract.

Manifestations of shock were observed in 38 and cyanosis in 36 instances.

The features of hemoptysis and cough (7 and 5 respectively) were evident in less than 10 per cent of the attacks and, with one exception, were limited to the minority of cases of longer standing or of repeated pulmonary embolism in which actual infarction of the lung was present.

Duration of Pulmonary Embolism. Attacks

of pulmonary embolism persist for a matter of minutes, hours, or days, and are usually fatal if the embolus is large. It may be said to be the rule that the larger the embolus or mass of emboli, the shorter and more likely fatal the attack.

In this series, the duration of the terminal attack may be tabulated by time intervals in 93 of the 100 cases. In 91, death occurred in

TABLE IV
DURATION OF FATAL ATTACK

Time	No. of Cases
Less than 5 minutes.....	33
From 5-30 minutes.....	29
From 30-60 minutes.....	10
From 1-24 hours.....	19
Total.....	91

less than 24 hours; the majority (72) did not survive over one hour (Table IV). Two patients had typical attacks and then went downhill gradually, one dying 8, the other 31 days later. In 10 cases there was evidence of pulmonary embolism prior to the terminal attack (Table V).

Incidence and Location of Pulmonary Infarcts. The incidence of pulmonary infarction in this series, as seen at autopsy, was 33 per cent. The location of the infarcts has been analyzed insofar as information allowed. They were limited to single lobes in 19 of the 33 cases, and were multiple in 14. The right lung was the site of infarction in 24 cases, while the left lung was involved in only 9. Localization of infarction in the lower lobe was demonstrated in all except 1 case.

Twelve cases with pulmonary infarcts were without history of pain in any location, while 15 were without that of pain in the chest. Pulmonary infarction was demonstrated in only 18 of the 33 cases in which chest pain was a symptom, so in 15 there appeared to be no relationship between pain in the chest and infarction.

Eight of the 9 patients with pain in the

chest previous to the terminal attack had pulmonary infarcts, but 5 of these had no hemoptysis. Pulmonary infarction was present in 10 and hemoptysis in only 2 of the 24 cases in which pain in the chest occurred only in the terminal attack.

Site of the Embolus. The terminal massive pulmonary embolisms viewed at autopsy were without the definite pattern of distribution within the major pulmonary vessels which was characteristic of infarcts when embolism had occurred earlier. (See figures 1 and 2.)

The Heart. An evaluation of a possible role of cardiac failure or enlargement offers many difficulties. Records in 57 cases show great variation in weight of the heart. One weighed 620 gm.; 8 weighed between 450 and 500 gm.; 8 between 400 and 450 gm.; 10 between 350 and 400 gm.; 21 between 300 and 350 gm., or nearest to the weight of 316 gm., which is accepted as normal; while only 9 weighed less than 300 gm. The mean weight was 340 gm. Body weights were recorded in only some of the protocols.

To determine whether strenuous training for endurance and other conditions peculiar to this conflict may have affected the cardiovascular system is not within the province of

TABLE V
INTERVAL BETWEEN PRIMARY AND
TERMINAL ATTACKS

Time	No. of Cases
Less than 24 hours.....	2
From 1- 5 days.....	2
From 6-10 days.....	2
Over 11 days.....	4
Total.....	10

this paper. It is possible, however, that the figures might be appreciably different from what would be found in a similar group of the same age and physical standard without military training.

Dilatation of the right ventricle was described in 27 cases; however, such an ob-



FIG. 1. Emboli in pulmonary arteries, demonstrated in situ in gross specimen.
Photograph AIP Acc. 97602

servation is all too frequently made by prosecutors without adequate evidence. Measurements of tricuspid and pulmonary valves suggest some increase in size; but the records are again incomplete, with figures for only 37 and 33 respectively. Considerable variation in measurements are inevitable because of the numerous pathologists involved. It is our opinion that it would be ill-advised to attempt to draw conclusions from such incomplete and inconsistent data.

Location of the Phlebothrombosis. Venous thrombosis, which may be regarded as the source of the embolism, was demonstrated in

62 cases, in which 113 separate thrombi were observed. In 46 the femoral vein or its tributaries were involved, and in 46 the iliacs, so that together they represent 81.4 per cent of the entire number.

The greater prevalence of thrombosis in the lower extremity has been reported rather consistently and has some foundation on experimental evidence.⁸ It has been demonstrated that throttling the blood flow by double partial ligations produced thrombosis in 13 of 22 experiments on the femoral vein in dogs, while only 1 small thrombus was produced in 14 instances of similar interference with circula-

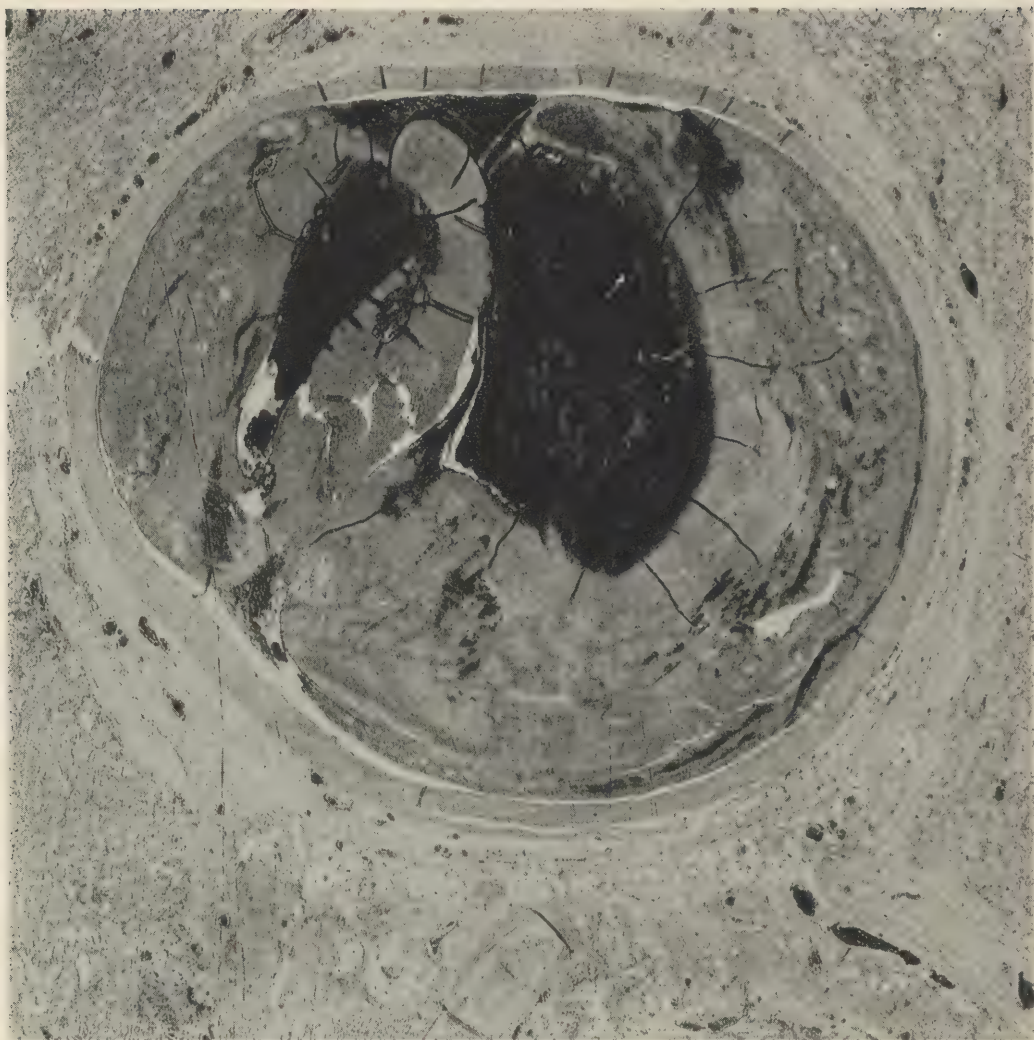


FIG. 2. Embolus coiled in pulmonary artery demonstrates eccentric pattern of lamination under low power. Photomicrograph AIP Acc. 6122.

tion through the external jugular vein. It was believed that impossibility of exercising the legs in the cramped quarters of the cage was responsible for femoral thrombosis; however, as the dogs were able to move their heads freely, the jugular veins were almost free of thrombi.

In our series the left side predominated as the location of the phlebothrombosis even though there were more wounds and fractures on the right side. Most significant is the striking localization of thrombosis of veins on the left in cases of single penetrating wounds of the chest indicated by 5 instances on that side,

with none on the right except once when thrombi were bilateral. The splinting of the diaphragm and stasis in the circulation of the lower extremity are the primary factors in the absence of localized trauma in these cases.

It appears that thrombosis is as likely to occur on the left as on the right in cases of wounds of the right lower extremity, but in the small number of single wounds on the left, thrombosis was found on the right only once and then it was bilateral. One may observe that there is a tendency for thrombosis to occur in the more central vessels in cases of abdomi-

nal wounds. Perhaps this is due directly to trauma or to infection when there are lacerations of the bowel.

In only about 10 per cent of the cases had there been forewarning of possible thrombophlebitis, and in these the venous thrombosis follows the pattern described by Ochsner and DeBakey¹² and appears to be consistent with the conception of Homans.^{13, 14}

Relationship of Anatomic Considerations to the Thrombosis. The predominance of thrombosis on the left in veins of the lower extremi-

ing the stream, and explains the well-known frequency of thrombosis in the left lower limb." A further agreement between the findings in the present study and his observations lies in the striking predominance of left-sided thrombosis at the level of the iliacs (internal and external). Aschoff continues, "The thrombosis on the right side extends up to Poupart's ligament, whereas on the left side it extends up to the point of compression of the left iliac vein by the right iliac artery."

The analysis by Dietrick¹⁶ of thrombosis fol-

TABLE VI
LOCATION OF THROMBI*
(Relationship to Crossing of Common Iliac Vein Behind Artery)

	Right	Not Stated	Left
Iliacs (Portion not stated) Common Iliac Vein	4 } 7 } ¹¹	4 } 0 } ⁴	5 } 6 } ¹¹
Internal Iliac Vein External Iliac Vein	2 } 1 } ³	2 } 0 } ²	10 } 7 } ¹⁷
Femoral Vein Tributaries of Femoral Vein	11 } 5 } ¹⁶	0 } 0 } ⁰	19 } 11 } ³⁰
Total	30	6	58

* (The figures are derived from total distribution data.)

ties in contrast to the greater frequency of wounds on the right is demonstrated by the findings in our series (Table VI). The anatomic basis for this striking disparity is fundamental and is found in the relationships and structure of the common iliac vein on the left. This vessel crosses behind the artery, passes over the sacrum to the right side of the vertebral column, thus running a longer and more oblique course than its fellow on the right.

Aschoff¹⁵ in 1924 stressed conditions favoring thrombosis, including an anatomic basis for localization. Our observations are in agreement with the concept he has expressed: "When lying on the back the increased compression of the left iliac vein by the arterial trunk (right iliac, middle sacral and left hypogastric arteries) has a direct influence in slow-

lowing battle casualties is of interest. It indicated the dominant role that trauma plays as a causative factor, whereas in peace time the factors of stasis and infection are the more prominent. The considerations of Aschoff and Dietrick apply to the general problem of thrombosis and are not limited, as in the present study, to cases of fatal pulmonary embolism. It cannot be concluded that post-traumatic infection has been absent in all cases of our series but it was not a notable feature.

It should be remembered that stasis as a factor in thrombosis is not limited to the aged and infirm, but is also incident to conditions of combat.

Summary. (1) One hundred cases of fatal pulmonary embolism in battle casualties are reported. They occurred in young, previously

healthy men and thus permitted observations without the usual variables and complicating factors of age and vascular disease.

(2) Venous stasis, caused most frequently by immobilization, appears to be the most important factor in the production of phlebotrombosis.

(3) Pulmonary infarcts were located predominantly on the right side and in the lower lobes.

(4) The prevalence of venous thrombosis on the left side of the body did not have a direct relationship with trauma which occurred more frequently on the right side.

(5) The distribution of the venous thrombosis seems to be based upon the anatomic relationships at the level of the common iliac vein.

REFERENCES

- ¹ Murnaghan, D., McGinn, S. and White, P. D.: Pulmonary embolism with and without acute cor pulmonale with especial reference to the electrocardiogram, *Am. Heart J.*, 25:573-597, 1943.
- ² McGinn, S. and White, P. D.: Acute cor pulmonale resulting from pulmonary embolism. *J.A.M.A.* 104:1473-1480, 1935.
- ³ Virchow, R.: Die Verstopfung der Lungenarterie und ihre Folgen. *Beitr. z. exper. Path. u. Phys. H.*, 2:1-90, 1846.
- ⁴ McCartney, J. S.: Postoperative pulmonary embolism, *Surgery*, 17:191, 1945.
- ⁵ McCartney, J. S.: Pulmonary embolism following trauma, *Surg. Gynec. & Obst.*, 61:369-379, 1935.
- ⁶ Vance, B. M.: Thrombosis of veins of the lower extremity and pulmonary embolism as complication of trauma, *Am. J. Surg.* 26:19-26, 1934.
- ⁷ The Medical Department of the U.S. in the World War, vol. XV, Statistics, Part 2, Medical and Casualty Statistics, War Department, 1925.
- ⁸ Potts, W. M. and Smith, S.: Pulmonary embolism, clinical and experimental study, *Arch. Surg.* 46:27-39, 1943.
- ⁹ Lister, W. A.: Causation of pulmonary embolism following operation, *Lancet*, 1:111-116, 1927.
- ¹⁰ Simpson, K.: Shelter deaths from pulmonary embolism, *Lancet* 2:744, 1940.
- ¹¹ Middleton, W. S.: Abdominal pain in pulmonary thrombosis, *Ann. Int. Med.*, 18:345-349, 1943.
- ¹² Ochsner, A. and DeBakey, M.: Thrombophlebitis and phlebothrombosis. C. Jeff Miller lecture, *South. Surgeon*, 8:269-290, 1939.
- ¹³ Homans, J.: Thrombosis of the deep veins of the lower leg, causing pulmonary embolism, *New England, J. Med.*, 211:993-997, 1934.
- ¹⁴ Homans, J.: *Circulatory Diseases of the Extremities*, New York, MacMillan, 1939.
- ¹⁵ Aschoff, L.: *Lectures on Pathology*, New York, Paul B. Hoeber, 1924. (p. 264).
- ¹⁶ Dietrick, A.: Die Thrombose nach Kriegsverletzungen. *Veroff. a.d. Geb. d. Kriegs u. Konstitution-pathologie.*, 1920, Heft 3.



INTRA-OCULAR TUMORS IN SOLDIERS, WORLD WAR II

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(With sixty-six illustrations)

TRUE intra-ocular neoplasms and other tumors which may be regarded as at least potentially neoplastic were found in 42 (1.08 per cent) of 3882 eyes of soldiers studied during World War II at the Army Institute of Pathology. The tumors were of particular interest because they occurred in a relatively homogeneous population, that is, in presumably healthy men 18 to 38 years of age. This paper deals primarily with the clinical manifestations and the histopathologic features of these neoplasms. The types encountered are shown in Table I, and they will be considered in the order in which they are listed.

TABLE I

Tumor	Number of Cases
Benign melanoma of the iris associated with malignant melanoma of the choroid*	7
Benign melanoma of the iris	2
Malignant melanoma of the iris	5
Benign melanoma of the choroid	6
Malignant melanoma of the ciliary body and choroid	25
Metastatic melanoma in the eye	1
Metastatic carcinoma in the choroid	1
Pseudo-adenomatous hyperplasia with dyskeratosis of an epithelial implant	1
von Hippel's hemangiomatosis	1

* Observed in 7 of the 25 eyes with malignant melanoma here listed.

BENIGN MELANOMA OF THE IRIS ASSOCIATED WITH MALIGNANT MELANOMA OF THE CHOROID

Small benign melanomas or pigment freckles of the iris were found in 7 of the eyes enucleated for malignant melanoma of the choroid. Whether the growths are true tumors, or whether they are malformations that may become neoplastic is still an open question. In most instances the cellular accumulations were very small and similar to those often seen in eyes without other tumors. In one instance, however, the growth appeared

to have caused ectropion uveae (Fig. 1), and in a case of bilateral metastatic malignant melanoma, reported later in this paper, benign melanomas of the iris (Fig. 41 and 42) were bilateral as well as larger and more deeply pigmented than in the other cases. Reese¹ regarded such growths, when associated with malignant melanomas of the uveal tract, as separate benign tumors rather than seedings from the malignant tumor.

BENIGN MELANOMA OF THE IRIS

Benign melanoma of the iris, not associated with other tumors, was present in two cases. In both of these, a pigmented lesion had been observed for 15 years and iridectomy was performed because of recent active growth. The tumors extended from the anterior surface deep into the posterior portion of the iris, and by slit lamp examination as well as in unbleached sections, had the appearance of possible malignancy (Fig. 2). However, in the bleached sections (Fig. 3) the sparse cellularity of the tumors indicated their benign character, and the eyes were not enucleated.

MALIGNANT MELANOMA OF THE IRIS

The oldest patient with malignant melanoma of the iris was 34, 4 others were in their twenties. The tumors had been observed for from one and a half to 5 years; 2 interfered with vision. Melanoma was diagnosed clinically in 4, and in 1 in which the growth was lightly pigmented the clinical diagnosis was leiomyoma. In this and one other instance iridectomy was performed before enucleation. In the first case (Fig. 4 and 5) microscopic sections revealed the nevoid type of cell and the nest-like arrangement characteristic of skin nevi. This is often seen in malignant melanomas of the iris, although it is rarely encountered in those of the choroid, and it does not fall into Callender's classification.^{2,3,4,5} In the second case the cells, al-

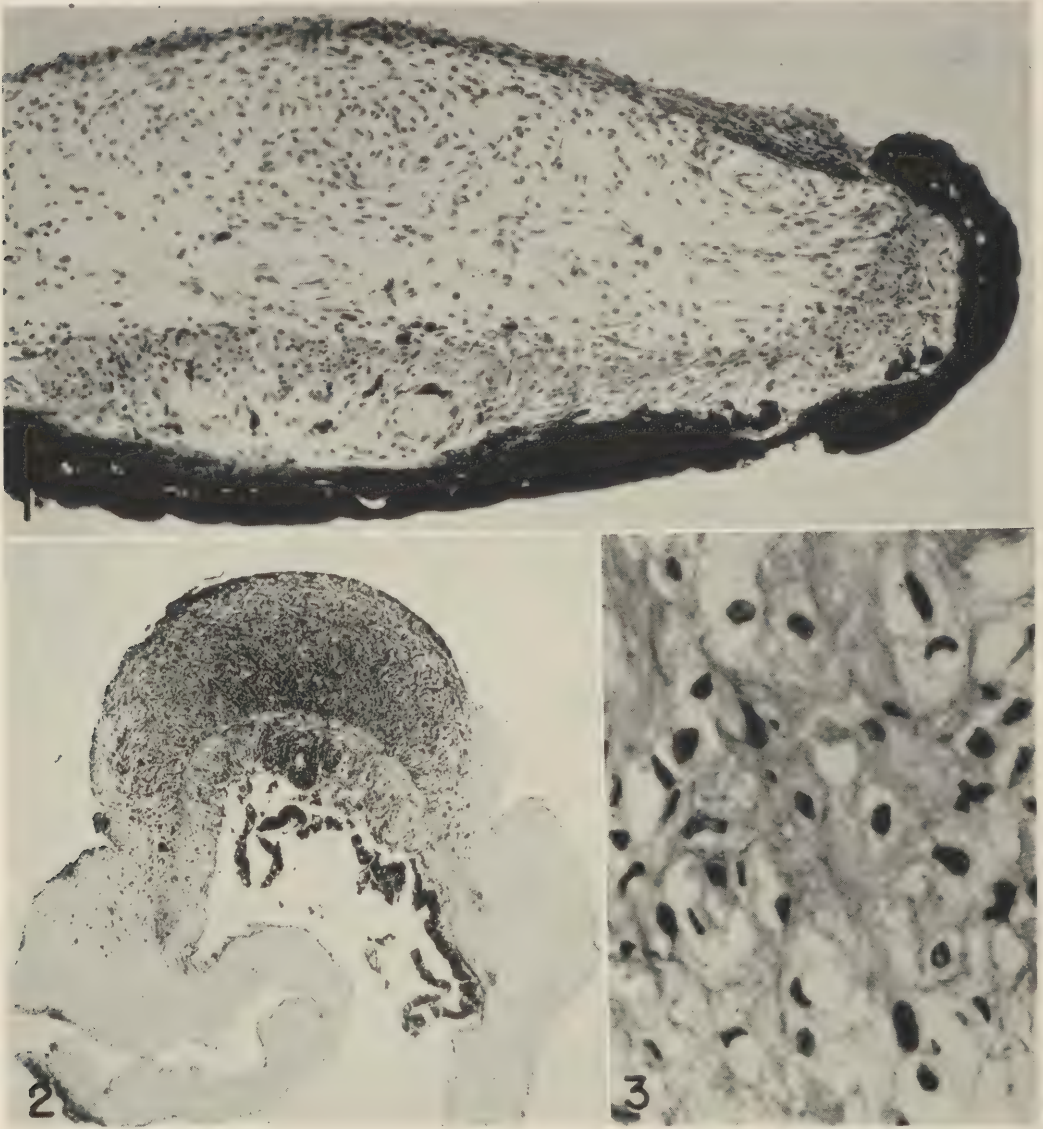


FIG. 1. Benign melanoma (pigment freckle) of the iris, causing ectropion uveae. $\times 100$. AIP Neg. 96124.

FIG. 2. Benign melanoma of the iris, removed by iridectomy. $\times 50$. AIP Neg. 95871.

FIG. 3. Bleached section, demonstrating the sparse cellularity of the tumor shown in Fig. 2. $\times 650$. AIP Neg. 95914.

though they retained their nest-like arrangement, were predominantly of the spindle B type of Callender (Fig. 6). Both tumors had extensively invaded the stroma of the iris. In the first case the eye was not submitted for microscopic examination. In the second case examination showed a residual tumor in the filtration angle on the side opposite that of operation (Fig. 7).

In 4 instances the filtration angle and anterior ciliary body were involved (Fig. 8), with tumor cells in the spaces of Fontana, canal of Schlemm, and in or around the vessels of the intrascleral plexus (Fig. 9). Occlusion of the filtration angle by tumor led in one instance to secondary glaucoma with cupping of the optic disc, but in the other eyes the tension was normal. In none of these tumors was

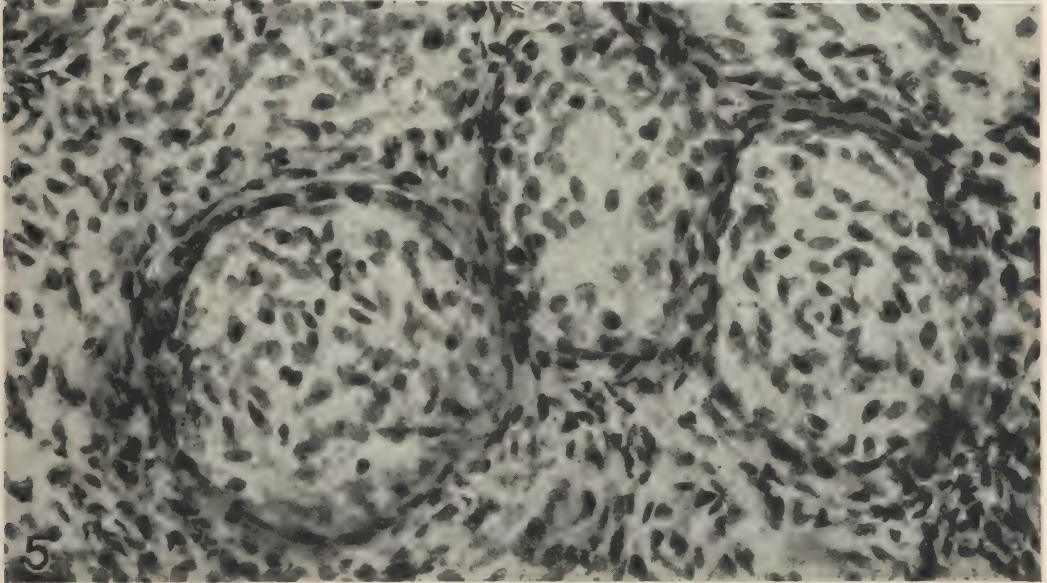
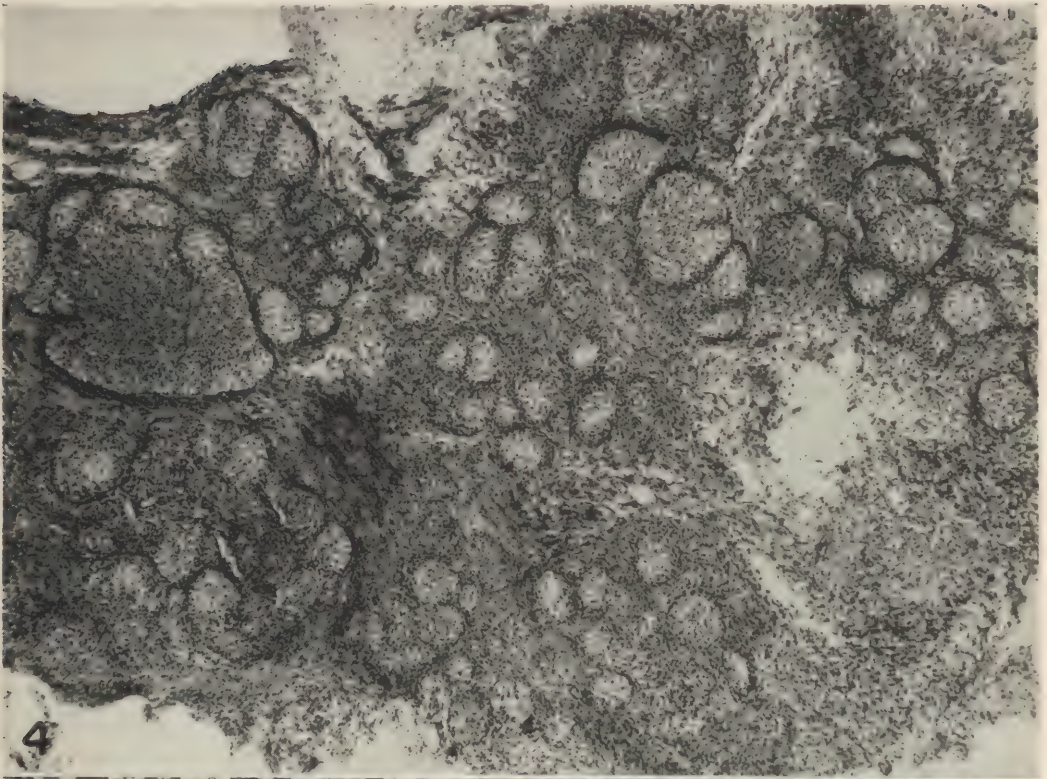


FIG. 4. Malignant melanoma of the iris removed by iridectomy. The tumor is densely cellular and invasive. $\times 60$. AIP Neg. 95881.

FIG. 5. Nevus type of cell and arrangement in tumor shown in Fig. 4. $\times 450$. AIP Neg. 95882.

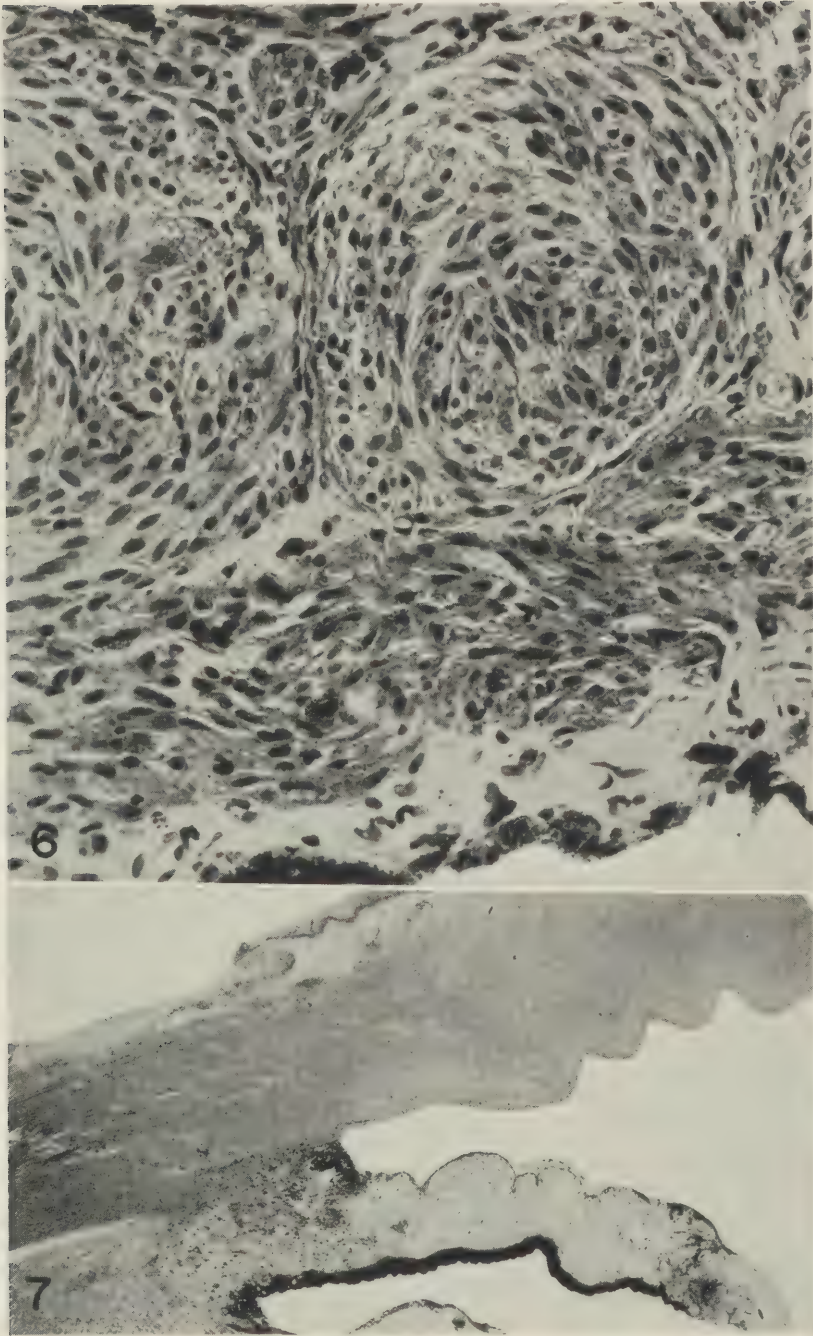
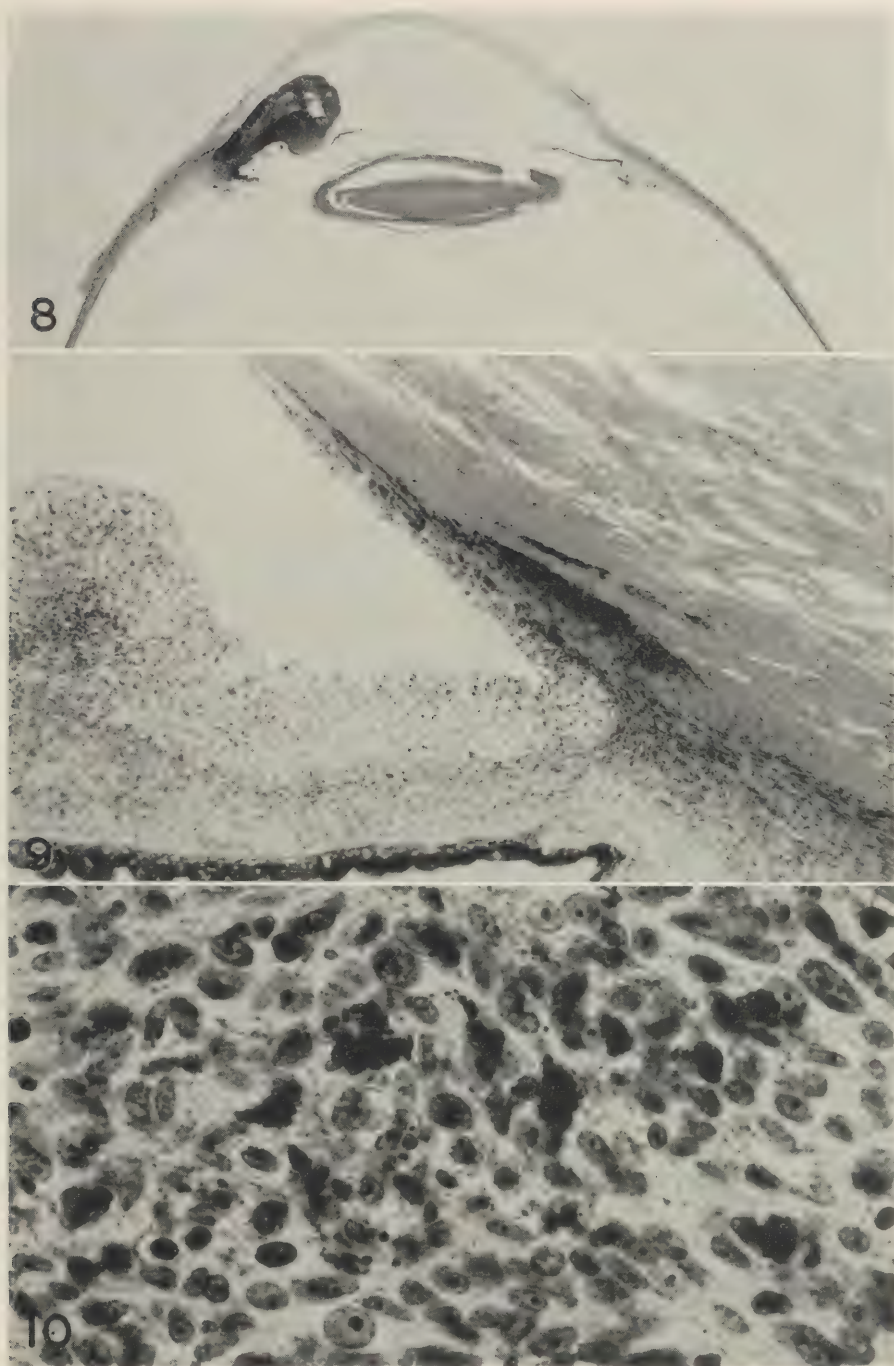


FIG. 6. Malignant melanoma of the iris removed by iridectomy. Nevoid arrangement of spindle-shaped cells. $\times 400$. AIP Neg. 95886.

FIG. 7. Tumor cells in the filtration angle on the side opposite that of iridectomy. The eye was enucleated following microscopic examination of the section shown in Fig. 6. $\times 35$. AIP Neg. 95888.

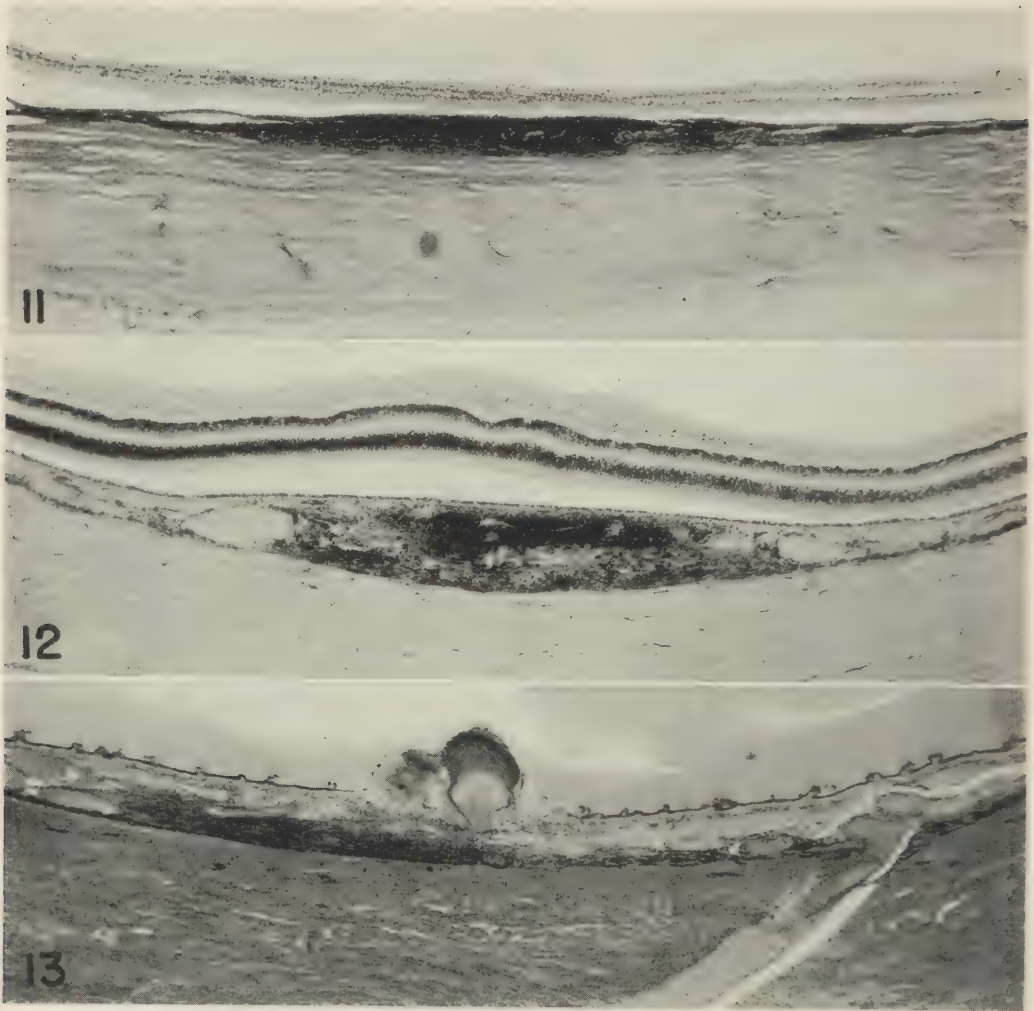


MALIGNANT MELANOMA OF THE IRIS

FIG. 8. Involvement of the anterior ciliary body and the filtration angle. AIP Neg. 95887.

FIG. 9. Tumor cells on the anterior surface of the iris, in the filtration angle, and around the canal of Schlemm and vessels of the intrascleral plexus. $\times 90$. AIP Neg. 95866.

FIG. 10. Mixed cell type: spindle cells, subtype B, and an occasional large epithelioid cell. $\times 650$. AIP Neg. 95880.



BENIGN MELANOMA OF THE CHOROID

FIG. 11. Incidental finding in an eye removed 6 months after penetrating injury. $\times 50$. AIP Neg. 95868.

FIG. 12. Incidental finding in an eye removed 3 months after penetrating injury. $\times 50$. AIP Neg. 95869.

FIG. 13. Incidental finding in phthisical eye enucleated 21 years after penetrating injury. Calcified drusen on Bruch's membrane. $\times 50$. AIP Neg. 95867.

extrabulbar extension seen. Microscopically, two of the tumors combined nevoid and spindle B type cells, and three were of the mixed cell type with spindle B and epithelioid cells predominating (Fig. 10).

BENIGN MELANOMA OF THE CHOROID

The 6 benign melanomas of the choroid were all incidental findings in eyes removed because of penetrating wounds. Five of the injuries had occurred in action or training and

the eyes were enucleated in from less than 24 hours to 6 months, but in the sixth case the injury had been incurred 21 years before enucleation of the phthisical eye. Histologically, the tumors appeared as deeply pigmented thickened areas in the posterior choroid (Fig. 11, 12 and 13). In bleached sections they exhibited different degrees of cellularity, some being sparsely (Fig. 14) and others more densely cellular. Although the tumor shown in Fig. 15 was much more cellular than that

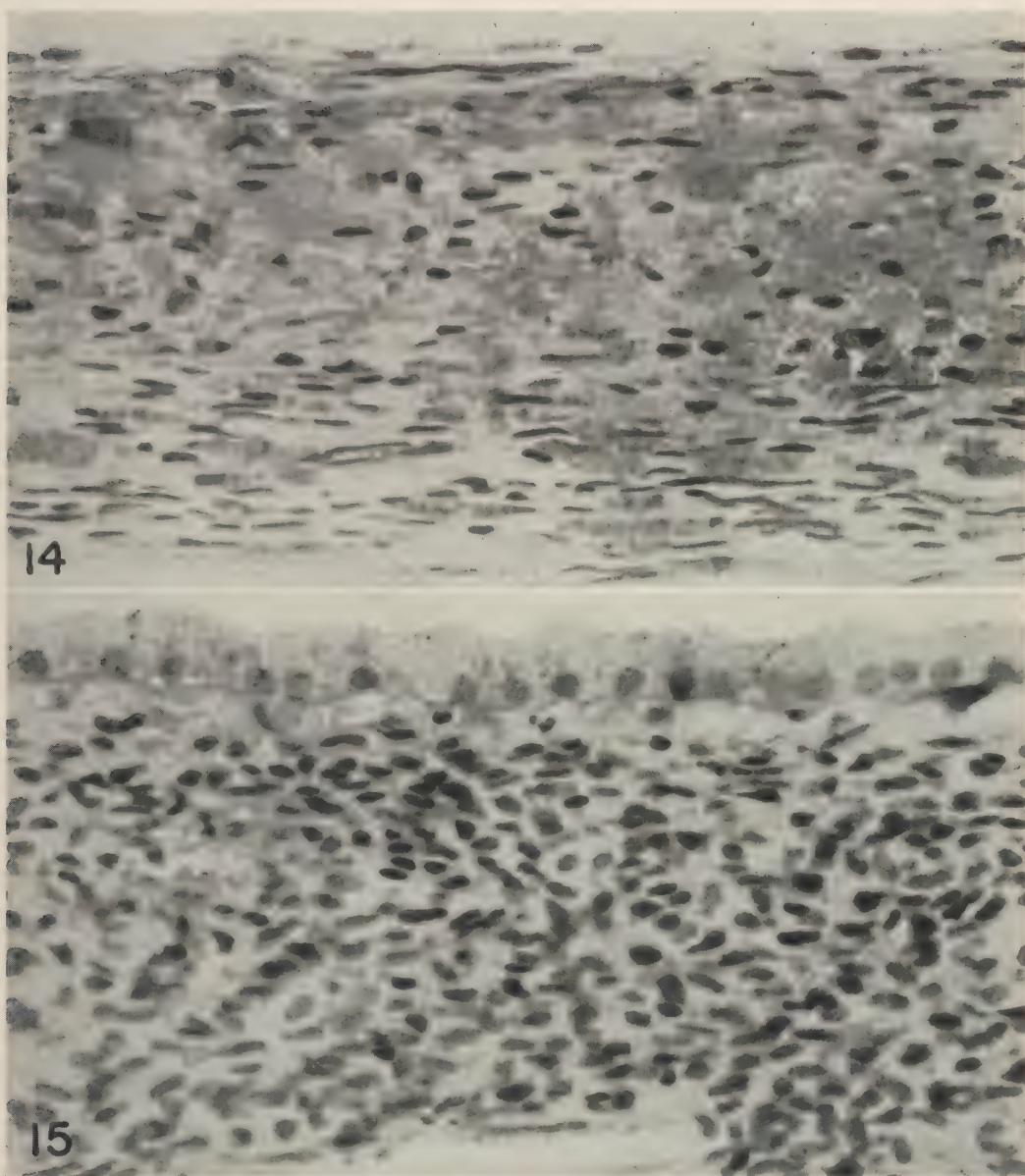


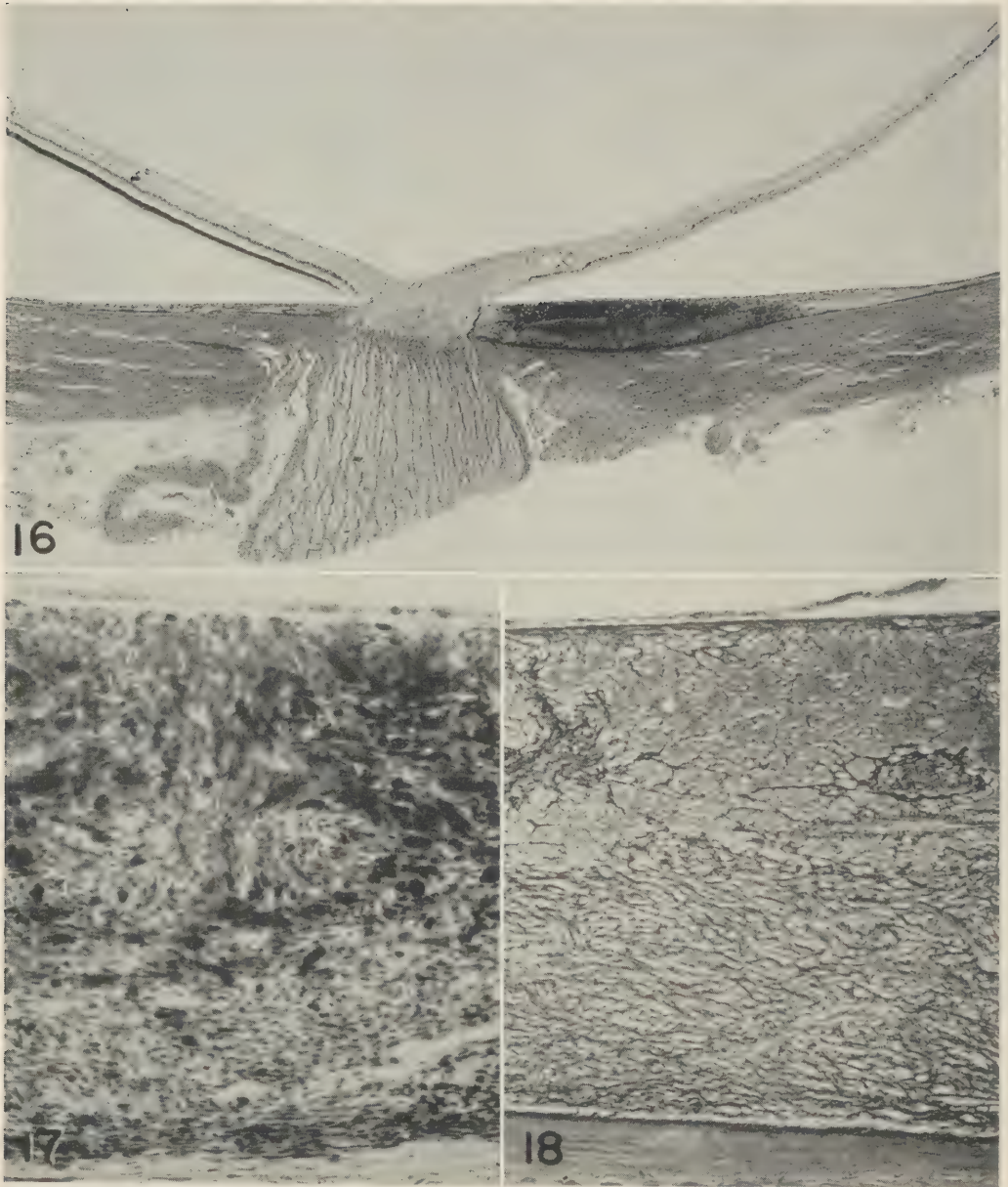
FIG. 14. Benign melanoma of the choroid, sparsely cellular. Bleached section. $\times 650$. AIP Neg. 95896.

FIG. 15. Benign melanoma of the choroid with nevoid cells. No invasion of the choriocapillaris. Bleached section. $\times 650$. AIP Neg. 95872.

in Fig. 14, it was limited anteriorly by the choriocapillaris and there was no invasion of that layer. The cells were either nevoid with irregular nuclei, or spindle shaped with long narrow nuclei which were usually homogeneous in appearance. Rarely an ill-defined nucleolus was seen.

MALIGNANT MELANOMA OF THE CILIARY BODY AND CHOROID

The malignant character of 24 of these 25 malignant melanomas was fully developed; in only one case was the tumor regarded as of low-grade malignancy. This small melanoma was first observed on ophthalmoscopic exami-



MELANOMA OF THE CHOROID. EARLY OR LOW GRADE MALIGNANCY

FIG. 16. Tumor adjacent to optic nerve head. Bruch's membrane intact. $\times 14$. AIP Neg. 95894.

FIG. 17. Spindle cell, subtype A. $\times 200$. AIP Neg. 96221.

FIG. 18. Argyrophil fiber content heavy, except in an area beneath Bruch's membrane. Wilder reticulum stain. $\times 200$. AIP Neg. 95891.

nation following contusion of the eye; enucleation was performed 23 days after the injury. The irregularly pigmented tumor (Fig. 16) in the choroid adjacent to the optic disc was composed of closely packed spindle shaped cells, sometimes arranged in bundles (Fig. 17).

The nuclei of the cells were seldom nucleolated, and little nuclear detail was seen. The tumor was much more cellular, however, than the benign melanoma shown in Fig. 15 and it involved all the layers of the choroid except Bruch's membrane which appeared in-

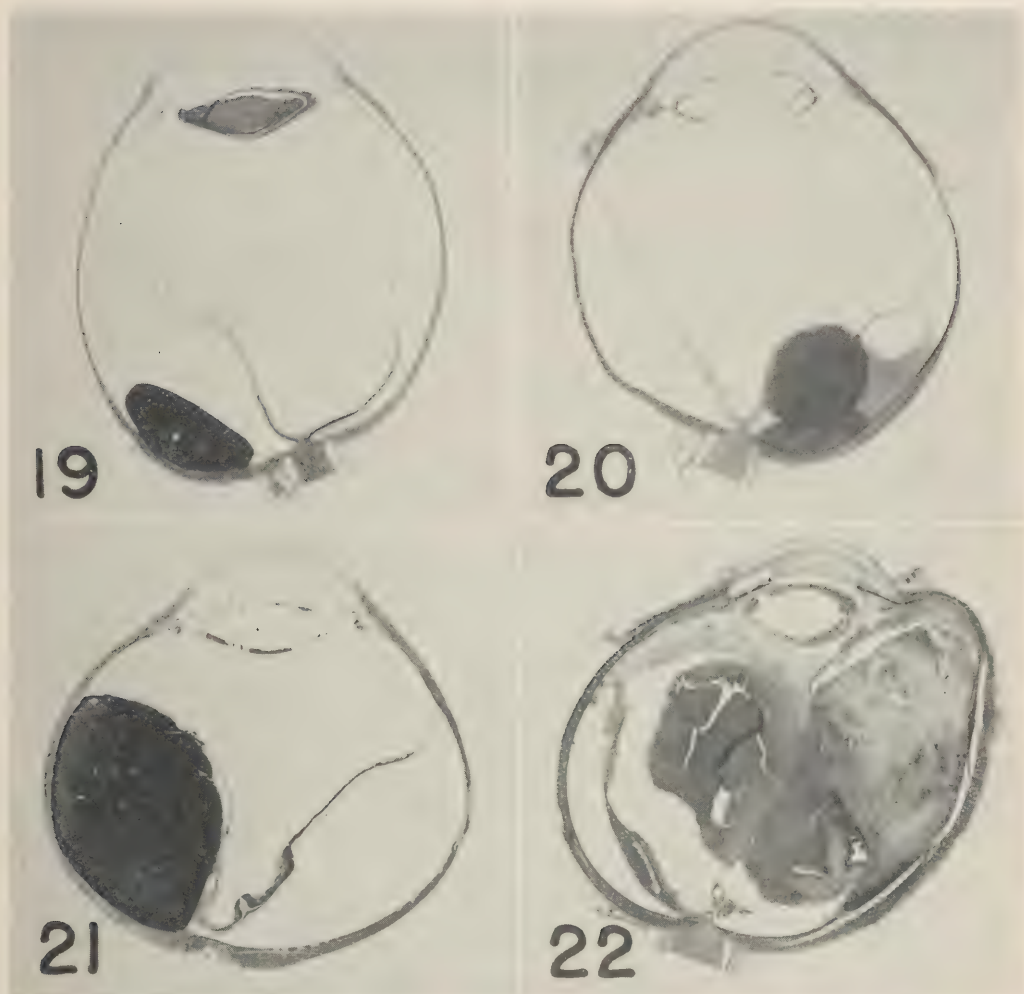


FIG. 19. Malignant melanoma of the choroid. Bruch's membrane intact. AIP Neg. 95873.

FIG. 20. Malignant melanoma of the choroid which has broken through Bruch's membrane and invaded the overlying retina. There is serous detachment of the adjacent retina. AIP Neg. 95874.

FIG. 21. Malignant melanoma of the choroid. Bruch's membrane intact. AIP Neg. 95876.

FIG. 22. Malignant melanoma of the ciliary body and choroid. Intra-ocular hemorrhage followed contusion 6 months before enucleation. AIP Neg. 95877.

tact. Argyrophil fibers⁶ were abundant throughout a large part of the tumor, indicating a low grade of malignancy (Fig. 2, 3, 4, 5); in the inner and apparently more active portion, where the protective mechanism of reticulum formation had been unable to keep pace with the growth of the tumor, there were nonfibred areas (Fig. 18). The retina over the tumor was atrophic and its rods and cones had disappeared but there was no exudate beneath it. Detachment, apparent in Fig. 16, occurred during the technical procedures.

Symptoms in the 25 cases were noted from 3 weeks to 11 years before enucleation; in 2 instances the tumors were found on routine examination. Loss or disturbance of vision was the usual symptom first to manifest itself and was recorded in all but 4 instances. Pain was recorded in 4 cases in 2 of which there was glaucoma, in the other 2 intra-ocular hemorrhage. Two patients had multiple moles, one on the axillae and buttock, the other on the back. The urine was negative for melanin in the 3 patients on which this test was recorded.

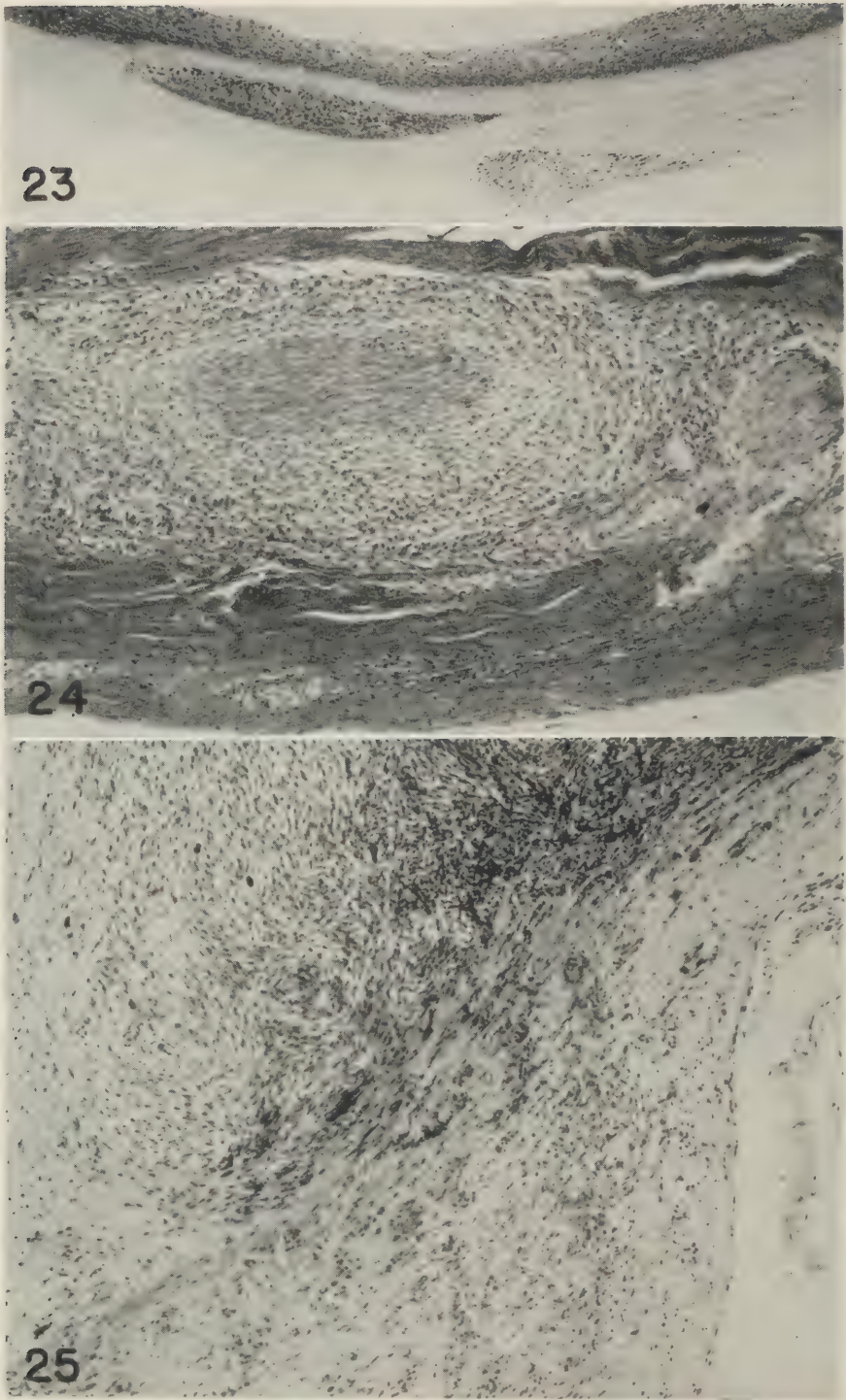


FIG. 23. Malignant melanoma of the choroid. Extension of the tumor through the sclera along the canal of a long posterior ciliary nerve and artery. $\times 30$. AIP Neg. 95911.

FIG. 24. Malignant melanoma of the choroid associated with a long posterior ciliary nerve in the scleral canal. $\times 150$. AIP Neg. 96125.

FIG. 25. Malignant melanoma of the choroid invading the nerve head and extending into the optic nerve. $\times 100$. AIP Neg. 96123.

A clinical diagnosis of tumor was made in 24 cases and, more specifically, of malignant melanoma or sarcoma in 20 in which the tumor was visualized on ophthalmoscopic examination. In 5 instances cataract, present in 2 eyes, or intra-ocular hemorrhage, present in 7 eyes, was of sufficient density and proportion to obscure the fundus (Fig. 22). In one of these the tumor was believed to be von Hippel's hemangiomas and, in the single instance in which no tumor was suspected, the eye was enucleated because of intra-ocular hemorrhage following contusion. Posterior sclerotomy, performed on both of these eyes, was followed by endophthalmitis; in one other case an operation for retinal detachment was performed with a subsequent diagnosis of tumor. Secondary glaucoma was observed in 4 eyes. Detachment of the retina (Fig. 20) was present in 24 eyes; in only one was detachment, at least around the tumor, absent.

Of the 25 malignant melanomas, the smallest (Fig. 16) measured 2.5 x 2.5 x 1.0 mm. and the largest 17 x 15 x 15 mm. Sixteen involved the posterior choroid (Fig. 19 and 20), 2 the choroid at the equator, extending both anteriorly and posteriorly (Fig. 21), and 6 the ciliary body and choroid (Fig. 22). Three had extended outside the eye along the posterior ciliary nerves and vessels (Fig. 23). The close association of these tumors with the ciliary nerves is shown in Fig. 24, lending support to Dvorak-Theobald's theory⁷ of their origin from the sheaths of Schwann of the ciliary nerves. Four had extended into, but apparently not through, the sclera. One had invaded the nerve head and one the optic nerve beyond the lamina cribrosa (Fig. 25), but not beyond the line of excision. In 2 instances tumor cells were present in the sclerotomy wounds; in 9 the tumor had invaded the overlying retina (Fig. 20), and in

6 more it had broken through Bruch's membrane but the retina was uninvolved (Fig. 21). Some of the tumors had two or more modes of extension; only 6 were confined to the uveal tract (Fig. 19).

The group of malignant melanomas have been classified according to cell type,^{2,3,4,5} fiber content,^{3,4,5} and pigment content.⁵ Table II shows the distribution of the tumors by Callender's classification based on cell types (Fig. 26, 27, 28, 29).

TABLE II

Cell Type	Number
Spindle cell subtype A	2
Spindle cell subtype B	14
Fascicular	1
Mixed cell type	6
Too necrotic to classify	2
Epithelioid	0
Total	25

The preponderance of spindle cell types over those containing the less differentiated epithelioid cells does not follow the pattern of our earlier survey⁵ in which the more malignant mixed cell type predominates. Twenty-five cases is not a sufficient number on which to base conclusions, however, and similar studies were made on the larger civilian groups to determine whether or not there was any foundation for this apparent relation between age and type. Table III indicates that, although the preponderance of the less malignant types does not exist in the larger group, there is still a higher percentage of them at the military age than of tumors removed in the later decades.

Table IV shows the distribution of tumors of the Army series according to fiber content (Fig. 31, 32, 33, 34).

Although there is no preponderance of the more heavily fibered and apparently less malig-

TABLE III

Source	Age	Spindle cell Subtype A and B	Total	Per Cent of Spindle Cell Tumors
Army	18-38	16	35	64.0
Civilian	18-38	104	231	45.0
Civilian	Over 38	518	1491	34.7
		120	256	46.8

nant tumors over those with a lower fiber content it is seen in Table V that a higher percentage of the less malignant types is present in the earlier than in the later decades.

TABLE IV

Fiber Content	Number
Heavy	1
Marked	7
Medium	5
Light	11
Absent	1
	—
Total	25

DISCUSSION

Melanomas of the uveal tract were found in white soldiers only. This was to be expected because of the rarity of these tumors among Negroes as exemplified in our previous series

statement that the average age for tumors of the iris is lower than for those of the ciliary body and choroid. This observation and the fact that melanomas of the iris behave less malignantly than do those of the choroid appear to be explainable on the basis of easy visibility and consequent early recognition of the iris tumors. On the contrary, unsuspected benign melanomas are found in the choroid of eyes enucleated for other causes. Malignant melanomas of the choroid have been noticed for the first time on routine examination or called to the patients' attention by injury. They have been known to exist for years, causing only minor visual disturbances. It appears that such tumors may persist for a long time in their less malignant spindle cell forms; suddenly, however, they show increased mitotic activity and formation of epithelioid cells

TABLE V

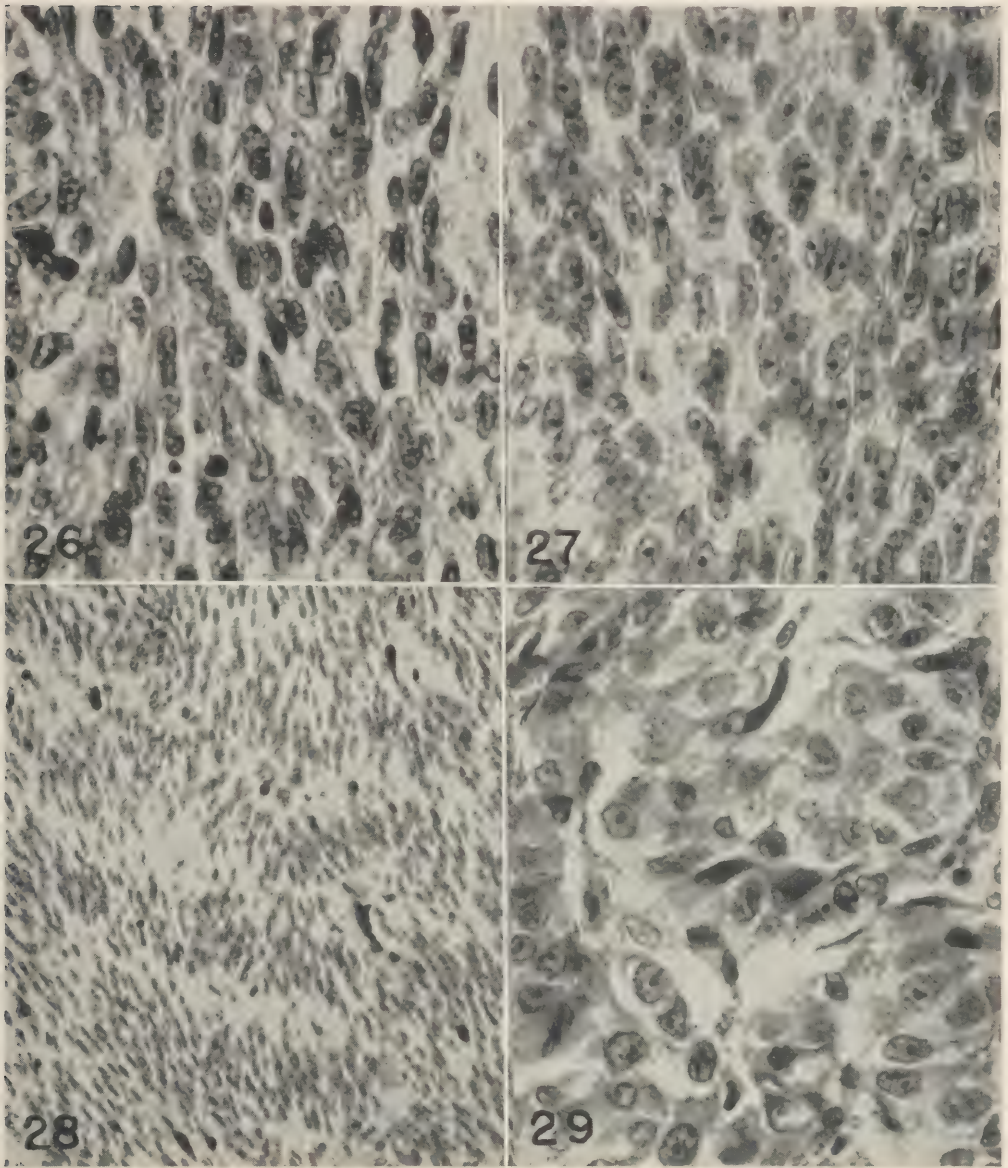
Source	Age	Fiber Content Heavy and Marked	Total	Per Cent of Heavily Fibered Tumors
Army	18-38	8	25	29.0
		78	256	30.4
Civilian	18-38	70	231	30.3
Civilian	Over 38	258	1491	17.3

of 1600⁵ malignant intra-ocular melanomas of which only 8 were in Negroes. In the present group the youngest soldier with melanoma was 19, the oldest 38, 23 were between 18 and 29, and 15 between 30 and 38 years of age. In the series of 1600 malignant melanomas just referred to, 240 or 15 per cent occurred in patients between the ages of 18 and 38. The addition of 370 received from civilian sources since June 1942 and 30 from Army sources now brings the total of melanomas of the eye on file in the American Registry of Pathology to 2,000. Three hundred fifteen or 15.75 per cent of these were in patients 18 to 38 years of age. The increased percentage of younger individuals in the more recent series, which includes Army cases, is so slight as to appear insignificant.

In a series of 137 malignant melanomas of the iris, including the 5 from the Army, 52 or 37.0 per cent were from patients under 40 years of age, which agrees with Duke-Elder's⁸

(Fig. 30). Studies, the results of which are presented in this paper, indicate that a higher percentage of the less malignant spindle cell and heavily fibered tumors is present in the earlier than in the later decades, and that epithelioid cells and tumors with a lower fiber content are more often encountered in eyes enucleated from patients over 40 years of age.

The foregoing observations are based on investigations of the collection of intra-ocular melanomas at the Army Institute of Pathology, and for the most part corroborate those of Duke-Elder in his masterly chapter on "Tumors of the Uveal Tract."⁸ These studies appear to justify the hypothesis that melanomas of the ciliary body and choroid which produce symptoms and metastasize are tumors predominantly of the higher decades, although, like the melanomas of the iris, they may exist in younger individuals as benign, quiescent, or slow growing forms more often than the clinical history suggests.



MALIGNANT MELANOMA OF THE CHOROID

FIG. 26. Spindle cell, subtype A. $\times 650$. AIP Neg. 95879.

FIG. 27. Spindle cell, subtype B. $\times 650$. AIP Neg. 95878.

FIG. 28. Fascicular type. $\times 200$. AIP Neg. 95892.

FIG. 29. Epithelioid cell type. $\times 650$. AIP Neg. 95884.

METASTATIC MELANOMA IN THE EYE

Melanoma, metastatic to both eyes from a primary site in the skin, represents such a rare condition that the one case in the present series deserves detailed consideration. The growth occurred in a 34 year old white soldier who had been through the North African,

Sicilian and Italian campaigns. The first symptoms, which led to the diagnosis of battle fatigue, were those of psychosis evidenced in his reaction to either friendly or enemy artillery fire. Physical examination, however, revealed several melanomas, having the appearance of buck shot, under the skin of the

abdomen and shoulders and on the left side of the face. There were also enlarged supraclavicular, axillary, epitrochlear, and inguinal nodes. Ophthalmoscopic examination disclosed fresh retinal hemorrhages but no intra-ocular tumor (Fig. 35, 36). The patient died with uremia during a blood transfusion a little over two months after the onset of symptoms.

At autopsy a malignant melanoma was found which involved the skin, bone marrow,

39). However, Bruch's membrane appeared intact. Tumor cells also packed veins in the ciliary body (Fig. 40) and in the iris (Fig. 41, 42). Another interesting feature in the iris was the presence of bilateral benign melanomas or pigment freckles (Fig. 41, 42) at the anterior surface of the pupillary zone. Tumor cells were present in and around the vessels of the intrascleral plexus (Fig. 45), in small veins in the conjunctiva, in veins of



FIG. 30. Malignant melanoma of the choroid, spindle cell, subtype B, with a mitotic figure and an epithelioid cell indicating recently increased activity. $\times 650$. AIP Neg. 95885.

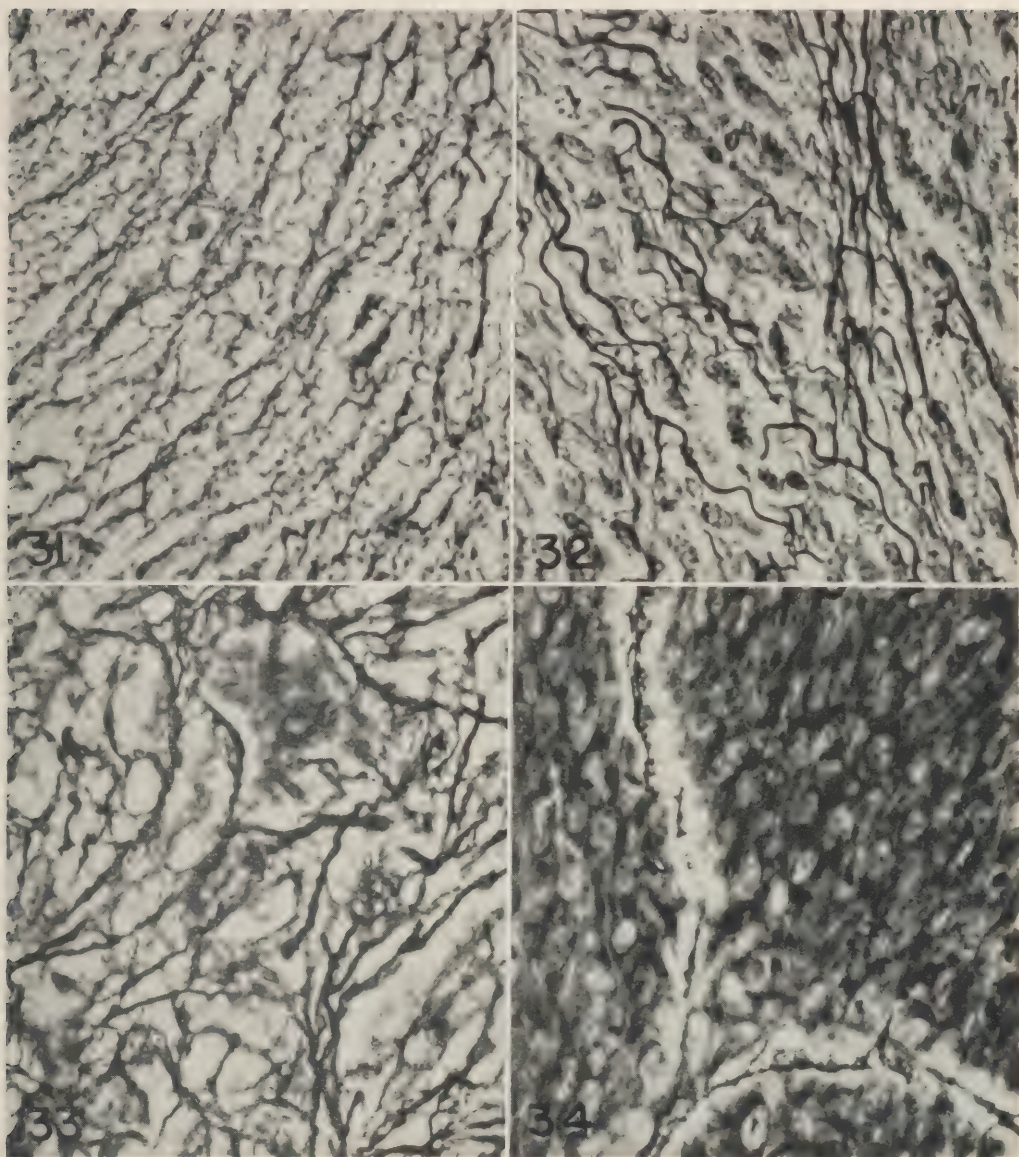
meninges, cerebrum, pericardium, heart, lungs, liver, spleen, pancreas, kidneys, mesentery and mesenteric lymph nodes. There was hematogenous seeding of the entire body. Veins plugged with tumor cells in the retina had given rise to the hemorrhages (Fig. 43, 44) which were noted on the ophthalmoscopic examination. Close to the macula, in the nerve fiber layer of the right eye, was a group of cytotoid bodies near a hemorrhage.

Most striking was the histologic appearance of the choroid in both eyes where large veins in the vascular layer and capillaries in the choriocapillaris were engorged with tumor cells (Fig. 37, 38). Tumor cells were rarely seen in the choroidal arteries (Fig. 38). For the most part they were confined within blood vessels, but in the peripheral choroid of both eyes they were present in the stroma (Fig.

the episclera, occasionally in the orbit (Fig. 46), and around small orbital arteries (Fig. 47).

Only one of the skin tumors (Fig. 48) was removed for sectioning. The tumor cells were in close association with nerve bundles deep in the dermis (Fig. 49) but no connection with the surface epithelium was seen. This tumor was not regarded as the primary tumor, although the clinical history and the distribution leave little doubt that the primary growth was in the skin.

The tumor cells in the skin, the eyes, and in all the metastases were similar. They were, for the most part, round or polygonal in shape, with abundant cytoplasm filled with finely granular brown pigment. Few spindle shaped cells were present. Irregularly shaped nuclei, rich in chromatin but with ill-defined nuclear



MALIGNANT MELANOMA OF THE CHOROID

FIG. 31. Heavy argyrophil fiber content. Wilder reticulum stain. $\times 650$. AIP Neg. 95862.

FIG. 32. Marked fiber content. In only a few areas are the tumor cells not surrounded by argyrophil fibers. Wilder reticulum stain. $\times 650$. AIP Neg. 95861.

FIG. 33. Marked fiber content but with small bundles of tumor cells not penetrated by argyrophil fibers. Wilder reticulum stain. $\times 650$. AIP Neg. 95863.

FIG. 34. Argyrophil fibers only in the interlobular stroma, none surrounding individual tumor cells. Wilder reticulum stain. $\times 650$. AIP Neg. 95864.

detail, gave the cells a nevoid appearance. Well-defined nuclei were rare, but occasional vacuolated nuclei and mitoses were seen. Large macrophages containing coarse pigment granules were observed in most of the metastases as shown in photomicrographs of the

liver (Fig. 50) and the bone marrow (Fig. 51). In the brain (Fig. 52) as in the retina, hemorrhages resulted from tumor emboli.

Both Fuchs⁹ and Parsons¹⁰ doubted that malignant melanomas, primary elsewhere, metastasize to the uveal tract. However, 10

cases in the literature are widely accepted as actual or possible instances of this condition. The cases of Brömser,¹¹ Schiess-Gemuseus and Roth,¹² Pflüger,¹³ Boente,¹⁴ Cordes and Horner,¹⁵ Corrado,¹⁶ Fry¹⁷ and Uhler¹⁸ appear to have been primary in the skin, although in Brömser's case this tumor was not examined microscopically, and in Pflüger's the eye was not enucleated, autopsy was re-

to be primary in the conjunctiva or lid of the left eye with metastases to the skin, brain and right ciliary body.

Another case of probable malignant melanoma metastatic in the eye, not reported formally but mentioned by Dr. Luther Peter in a discussion of Fry's case, was one in which multiple metastases followed a primary growth in the skin of the upper arm. The eye was



FIGS. 35 (O.D.) AND 36 (O.S.). Malignant melanoma metastatic in the eye, bilateral, from the skin. No gross tumor appears in either eye. AIP Neg. 96126.

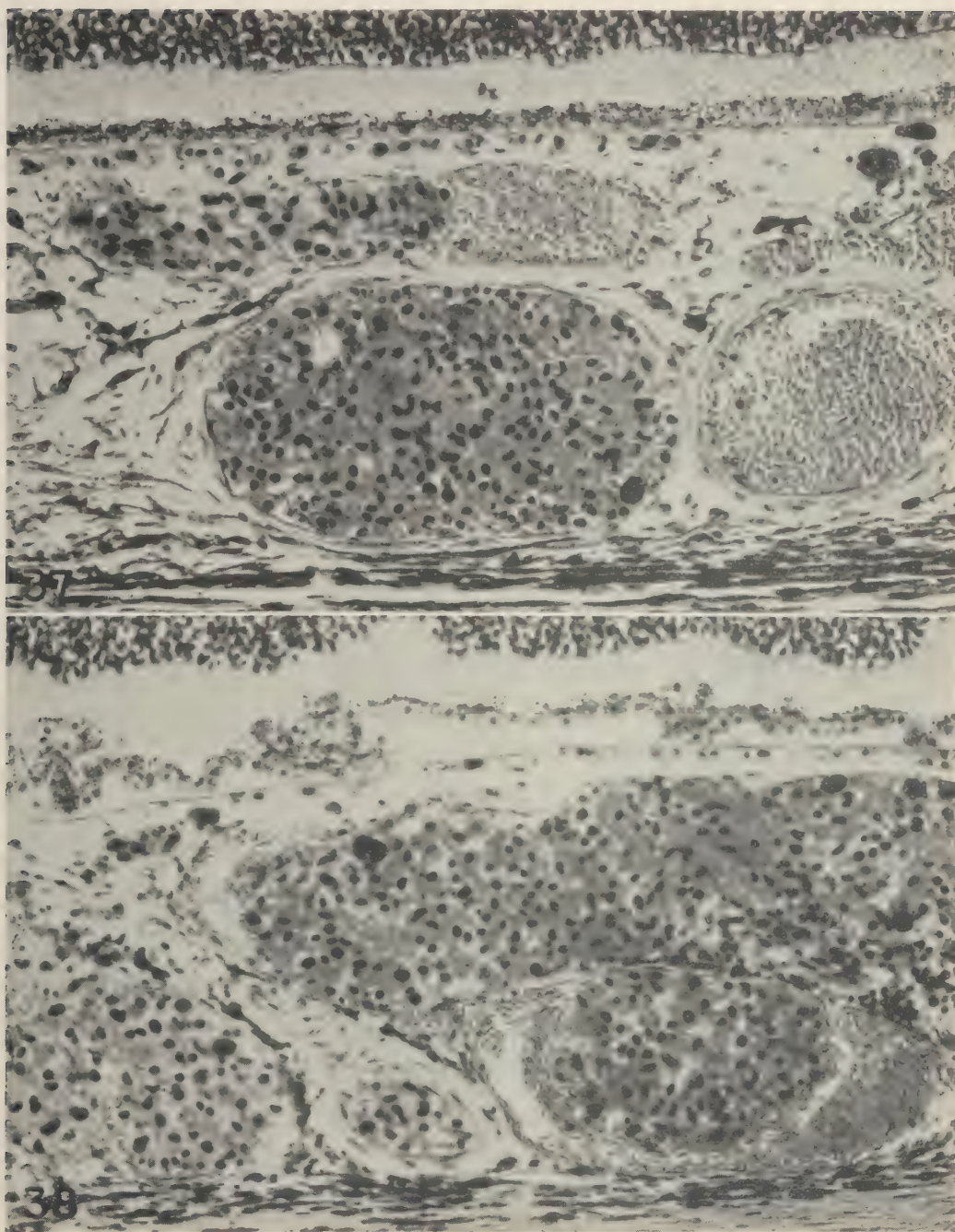
fused, and none of the lesions was subjected to microscopic examination.

The uveal tract was the site of metastasis in all but two instances: the case of Schiess-Gemuseus in which the nerve head and adjacent retina were involved and that of Uhler in which multiple metastases were present in the retina but none in the optic nerve. In Boente's case the tumor involved the choroid, retina, and optic nerve, and, as in ours, Bruch's membrane was intact. Tumor cells were noted in retinal veins in Boente's case and in a choroidal capillary in Fry's. Only in Cordes and Horner's case were the metastases to the eyes bilateral. There was however, bilateral involvement in ten Doesschate's²⁰ case in which the tumor is believed to have been primary in the right eye with metastases to the skin, the brain, and the choroid of the left eye. In the case of Adamük¹⁹ the tumor was believed

invaded only during the last 2 weeks of the patient's life but then growth was rapid. The same type cell was present in all lesions. The diagnosis was "sarcoma of the choroid."

METASTATIC CARCINOMA IN THE CHOROID

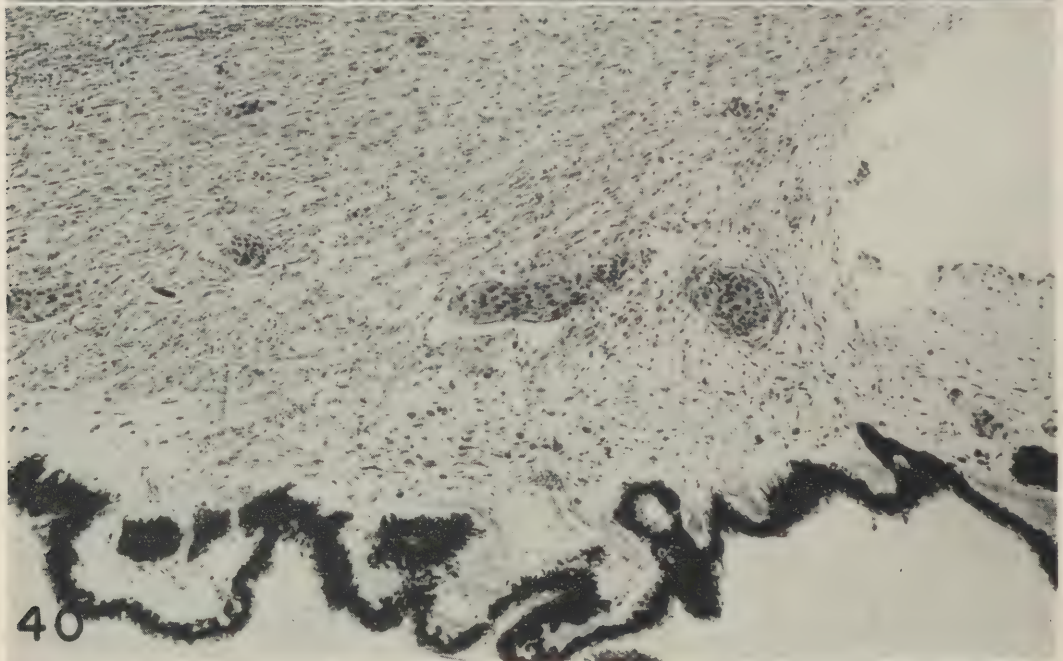
One other tumor, metastatic in the choroid bilaterally, less rare than the preceding one, was a papillary adenocarcinoma in a 33-year-old white soldier. The case is interesting in that the first symptom of disease was dimness of vision in the right eye. Soon after this a productive cough, night sweats, and a low grade fever developed for which the patient was hospitalized. A tumor of the right eye was discovered on examination; roentgenograms revealed lesions of the lungs, scapula, pelvis and spine. Because the first symptoms appeared in the right eye it was believed that this was the site of the primary tumor and



INTRA-OCULAR METASTASES FROM MALIGNANT MELANOMA OF THE SKIN

FIG. 37. O.S. Choroidal veins and capillaries engorged with tumor cells. $\times 250$. AIP Neg. 92872.

FIG. 38. O.D. Choroidal veins and capillaries and one artery engorged with tumor cells. $\times 200$. AIP Neg. 92870.



INTRA-OCULAR METASTASES FROM MALIGNANT MELANOMA OF THE SKIN

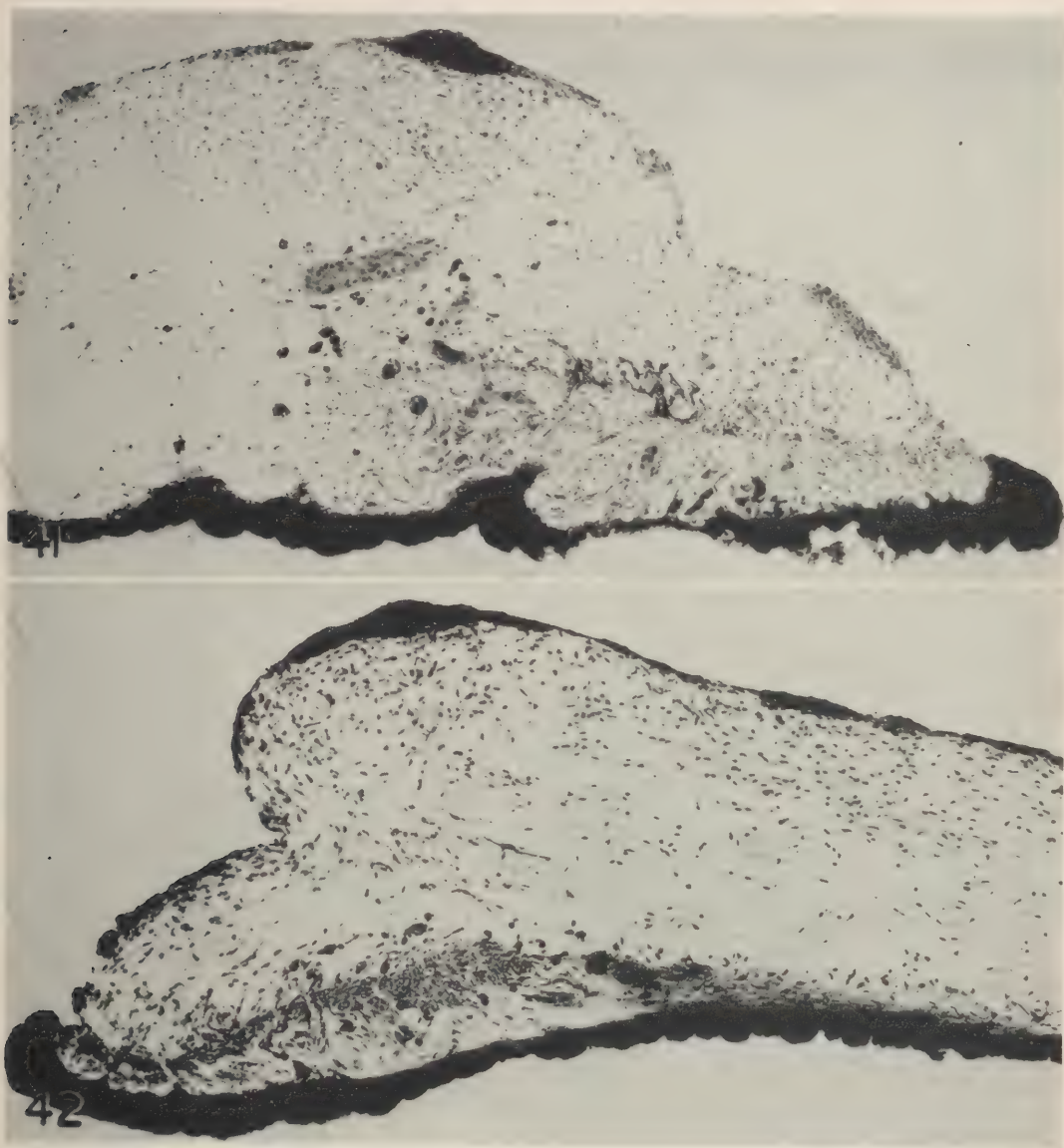
FIG. 39. Tumor cells in the peripheral choroidal stroma. Cystoid degeneration of the retina at the ora serrata. $\times 150$. AIP Neg. 92887.

FIG. 40. Tumor cells in the veins of the ciliary body. $\times 150$. AIP Neg. 92883.

that the generalized lesions were metastases of a malignant melanoma of the choroid. However, 10 months after the appearance of symptoms in the right eye, fundus changes were noted in the left eye. After this the course of the disease was complicated by Cheyne-Stokes respiration and left facial and right trochlear palsy. The patient died one

year after the onset of symptoms.

At autopsy, tumor of both lungs, particularly of the right lower lobe, was found with neoplastic invasion of the spleen, liver, adrenals, kidneys, brain, mesenteric, lumbar, and inguinal lymph nodes, the left 5th rib and the lumbar spine. Sections showed adenomatous neoplasm in the posterior choroid of both eyes



INTRA-OCULAR METASTASES FROM MALIGNANT MELANOMA OF THE SKIN

FIG. 41. Tumor cells in iris veins. Benign melanoma (pigment freckle) on the anterior surface of the iris. $\times 115$. AIP Neg. 92884.

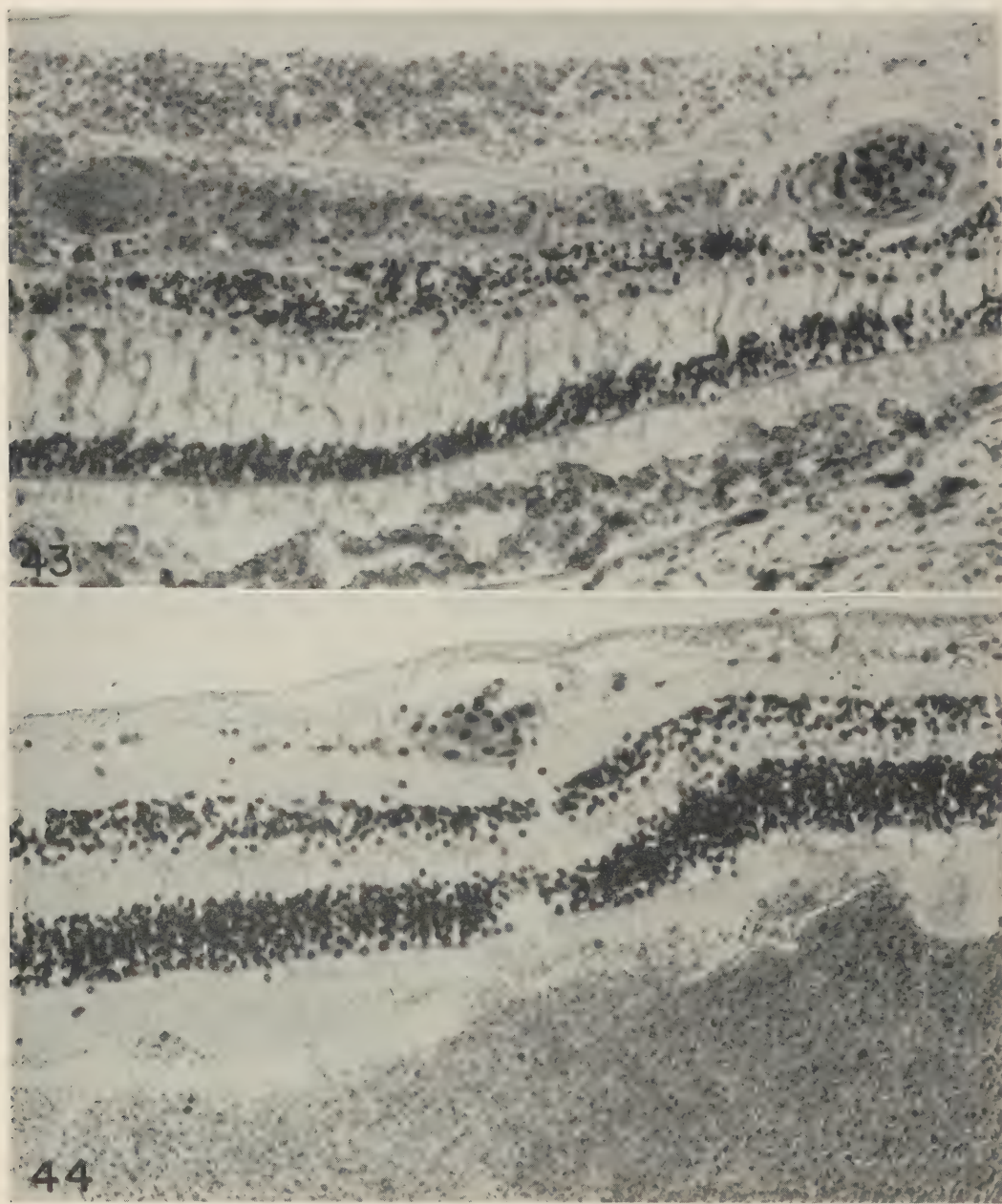
FIG. 42. O.S. Tumor cells in a vein in the region of the sphincter pupillae. Benign melanoma on the anterior surface of the iris. $\times 115$. AIP Neg. 92882.

(Fig. 53). Papillae projected into the alveoli which were lined by columnar epithelium (Fig. 54). A moderate number of mitoses was present (Fig. 55). The tumor in the other organs (Fig. 56, 57 and 58) was similar in appearance.

Histologically, both lung and gastro-intestinal tract must be given consideration as sites

of the primary tumor. However, multiple metastases, particularly to the brain, mesenteric lymph nodes, and bone, indicate that the primary site was more probably the lung.

The American Registry of Pathology now has a civilian series of 40 carcinomas metastatic in the uveal tract in which the age, sex and race are known: all were from white pa-



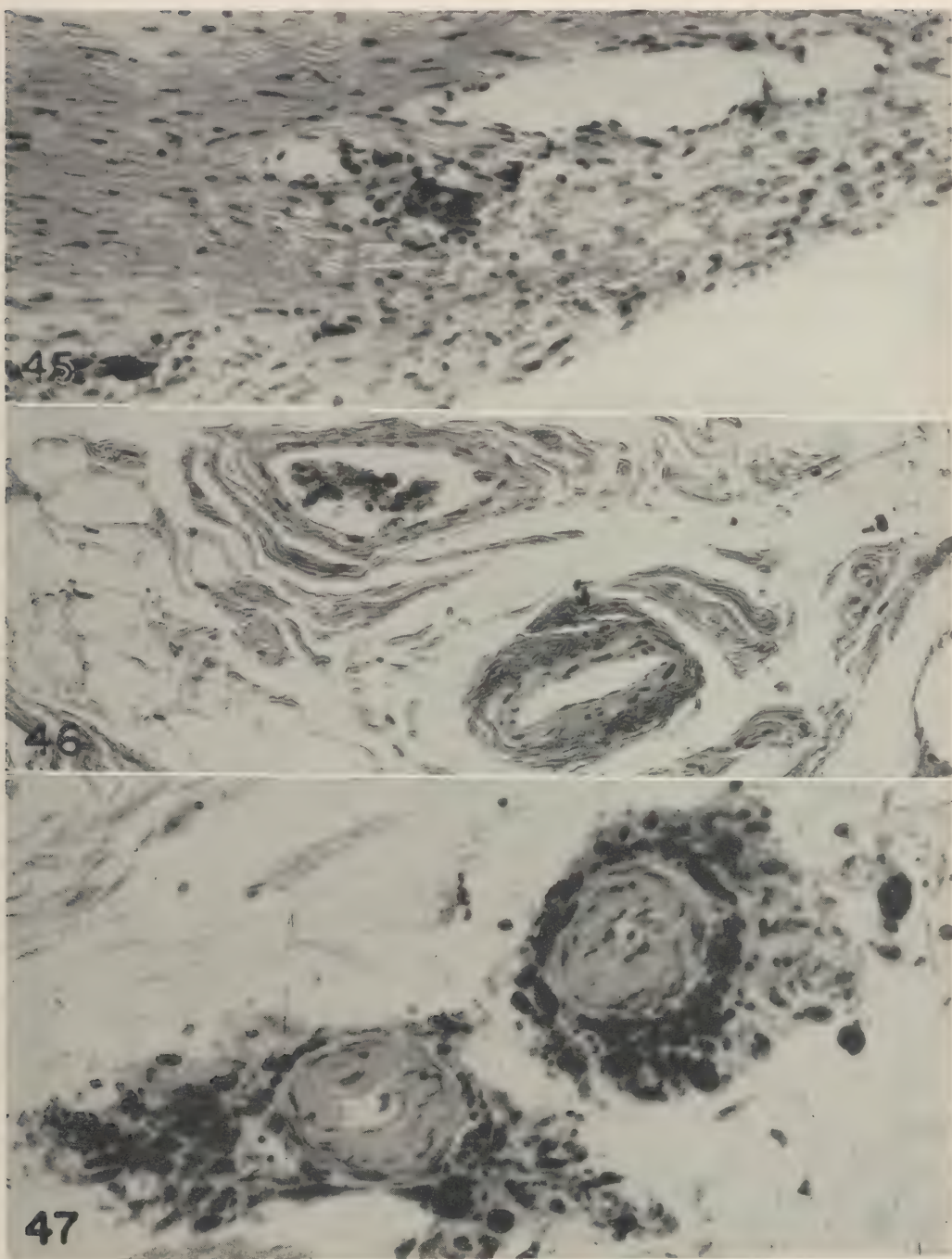
INTRA-OCULAR METASTASES FROM MALIGNANT MELANOMA OF THE SKIN

FIG. 43. O.S. Tumor embolus in a retinal vein causing hemorrhage in the nerve fiber layer. $\times 115$. AIP Neg. 92881.

FIG. 44. O.D. Tumor cells in a retinal vein. Subretinal hemorrhage. $\times 250$. AIP Neg. 92875.

tients, 28 from females and 12 from males. Only one patient was 33 years old; 5 others were in the middle or late thirties, and the rest were over 40. Breast, lung, gastro-intestinal tract, kidney, prostate, ovary and pancreas

are all represented as primary sites of the tumors, but next in frequency to the breast, the lung predominates as it did in Usher's²¹ series of 110 cases. In 4 of our 40 cases carcinoma of the eye was found before the



OCULAR METASTASIS FROM MALIGNANT MELANOMA OF THE SKIN

FIG 45. Tumor cells within the spaces of Fontana and in a vein near the canal of Schlemm. $\times 330$. AIP Neg. 92880.

FIG. 46. Tumor cells in an orbital vein. $\times 230$. AIP Neg. 92876.

FIG. 47. Tumor cells around orbital arteries. $\times 330$. AIP Neg. 92879.

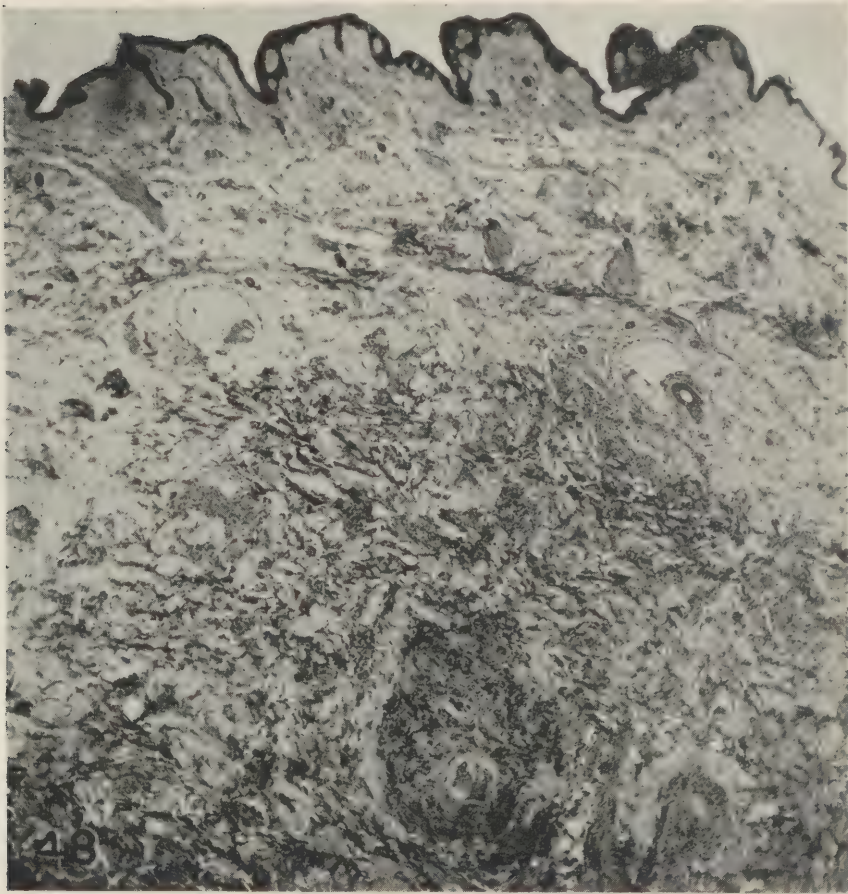


FIG. 48. Malignant melanoma of the skin with ocular metastases. This skin nodule was probably not the primary lesion. $\times 50$. AIP Neg. 95899.

primary tumor was suspected. In 2 of these it was in the lung, in 1 in the gastro-intestinal tract and in 1 in the breast. In 6 cases of carcinoma of the breast, metastases were first manifested in the eye. These were noted 12 years, 10 years, 9 years, and in 3 cases, less than 2 years after removal of the primary tumor. In 4 cases ocular metastases are known to have been bilateral.

Considering the age and sex incidence as well as the comparative rarity of this tumor, it is not surprising that only one should have been found among the eyes from Army sources. There is no feature of this case, however, age, sex, source, duration, symptoms, dissemination, or histopathology, that is not duplicated in our series of 40 from civilian sources.

PSEUDO-ADENOMATOUS HYPERPLASIA WITH DYSKERATOSIS OF AN EPITHELIAL IMPLANT

Although hyperplasia with dyskeratosis of an epithelial implant might not be considered true tumor, its behavior was so like that of a neoplasm that its inclusion in this series seems warranted. The eye came from a 22-year-old white soldier wounded in action; a magnetic foreign body was retained in the eye until enucleation, 16 days later. The foreign body, which measured $14 \times 8 \times 5$ mm., was lodged in the posterior segment and protruded through the sclera (Fig. 59). The globe was partially eviscerated, collapsed, and its remaining structures disorganized. Organizing hemorrhage and inflammatory tissue filled the globe and subacute endophthalmitis was evidenced by the presence of lymphocytes, plasma

cells, and polymorphonuclear leukocytes. The blocked areas in Fig. 59 were the sites of implanted surface epithelium, probably conjunctival rather than corneal. One (A) was in the ciliary region and the other (B) in the posterior segment near the site of the foreign

interesting to speculate if frank malignancy might have resulted had the eye not been enucleated. It is more probable that retrogression would have occurred or, as scar tissue developed, the growth would have been choked off.

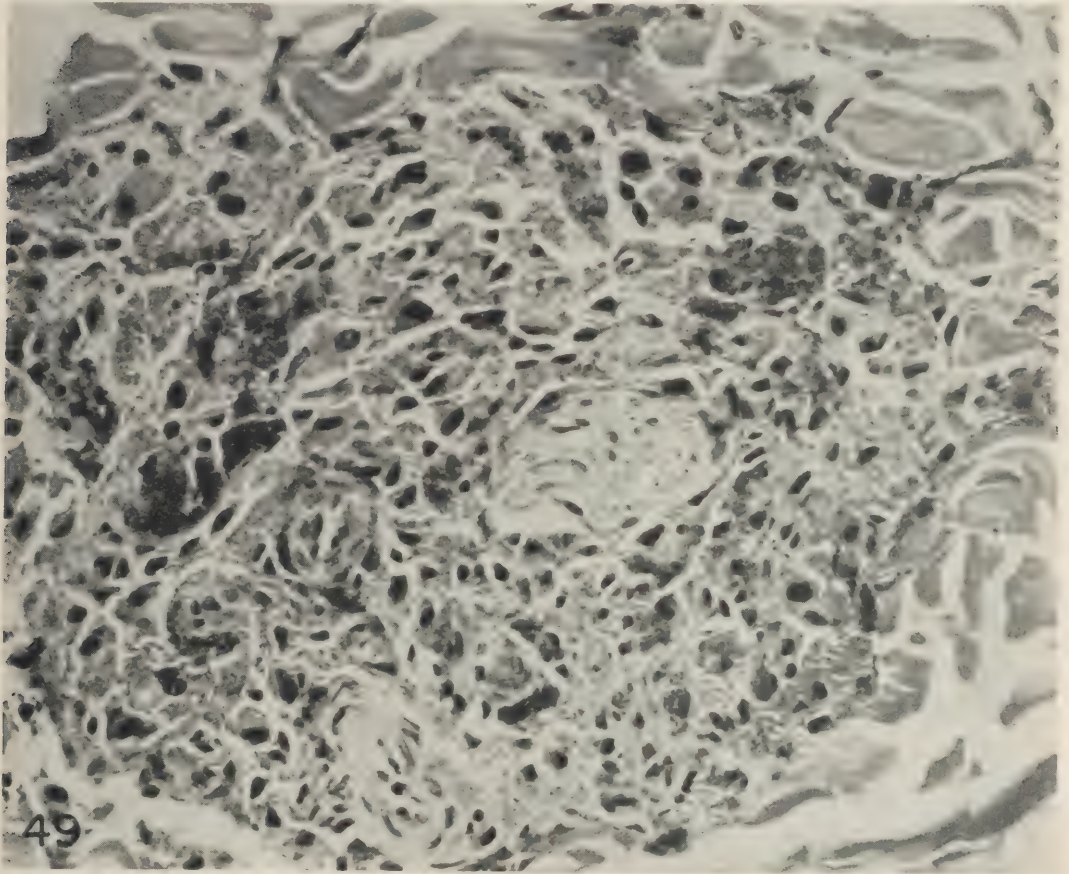
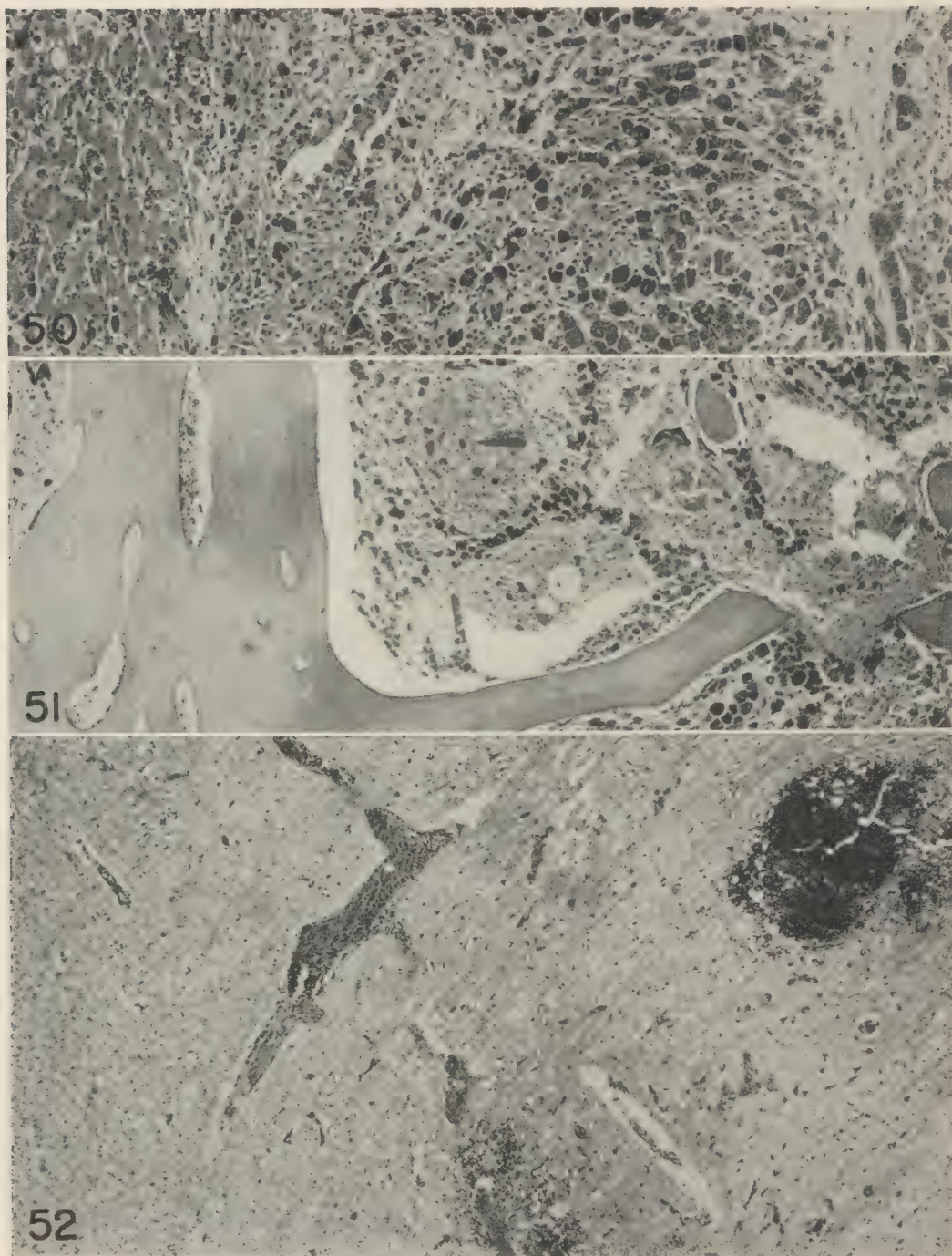


FIG. 49. Malignant melanoma of the skin with ocular metastases. Tumor cells in association with a nerve bundle in the dermis. $\times 450$. AIP Neg. 92874.

body. The implants showed hyperplasia and acanthosis (Fig. 60, 61) with abundant intracellular kerato-hyalin and the formation of epithelial pearls. Intercellular bridges were apparent (Fig. 61). Basal palisading was almost entirely absent (Fig. 62), and there appeared to be actual invasion where nests of epithelial cells were present beneath and separated from the larger mass.

The condition has been classified as a pseudo-adenomatous hyperplasia of epithelial implants, but in view of the dyskeratosis it is

The behavior of the implanted epithelium in this case is reminiscent of Lucké and Schlumberger's²² experiments on autotransplantation of epitheliomas of the lip and mouth of catfish into the anterior chamber of the eye. In 10 of 14 instances the transplanted tumor grew and vascularized in its new location, sometimes with actual invasion of the iris; however, after 2 months it became stationary and eventually regressed. Greene²³ and other investigators of tumor immunity have also found the anterior chamber a fertile

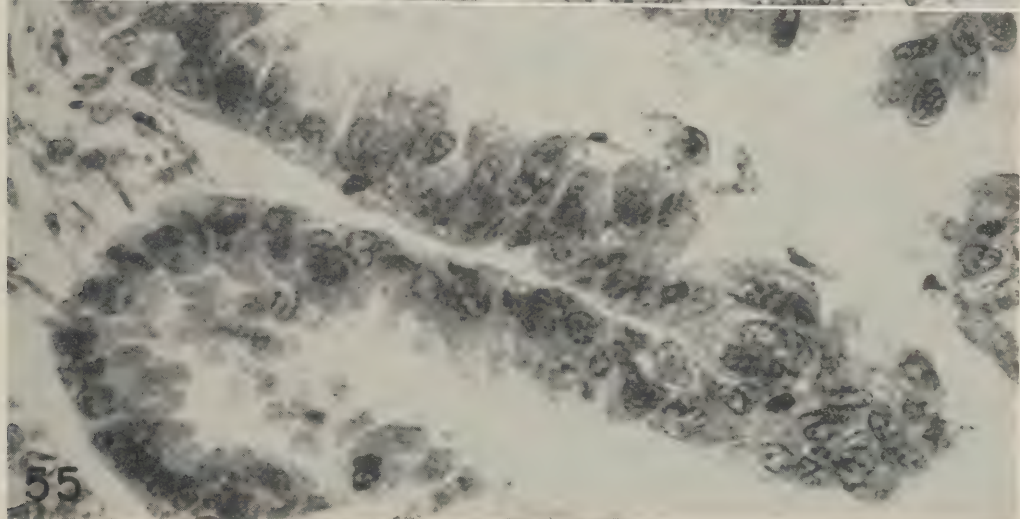
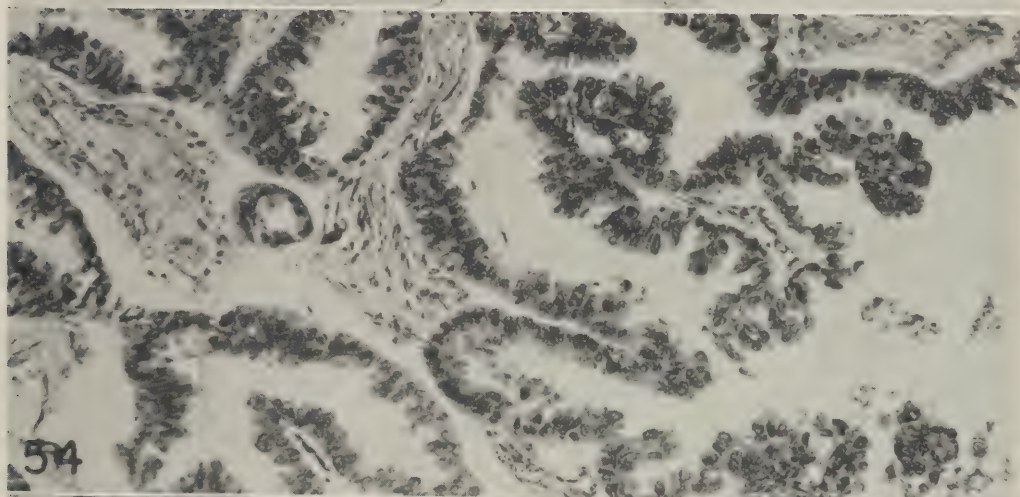


GENERALIZED MELANOMATOSIS FROM MALIGNANT MELANOMA OF THE SKIN

FIG. 50. Metastasis to the liver. The large dark cells are pigment-laden macrophages. $\times 140$. AIP Neg. 92873.

FIG. 51. Metastasis to the rib. Pigment-laden macrophages are also apparent here. $\times 160$. AIP Neg. 92885.

FIG. 52. Metastasis to the brain. Cerebral hemorrhages resulting from tumor emboli. $\times 75$. AIP Neg. 92886.



PAPILLARY ADENOCARCINOMA IN THE CHOROID, METASTATIC FROM THE LUNG

FIG. 53. Metastasis in the posterior choroid. $\times 10$. AIP Neg. 95903.

FIG. 54. Columnar epithelium lining alveoli. $\times 200$. AIP Neg. 95906.

FIG. 55. Columnar epithelium with mitoses, covering a papilla. $\times 500$. AIP Neg. 95905.

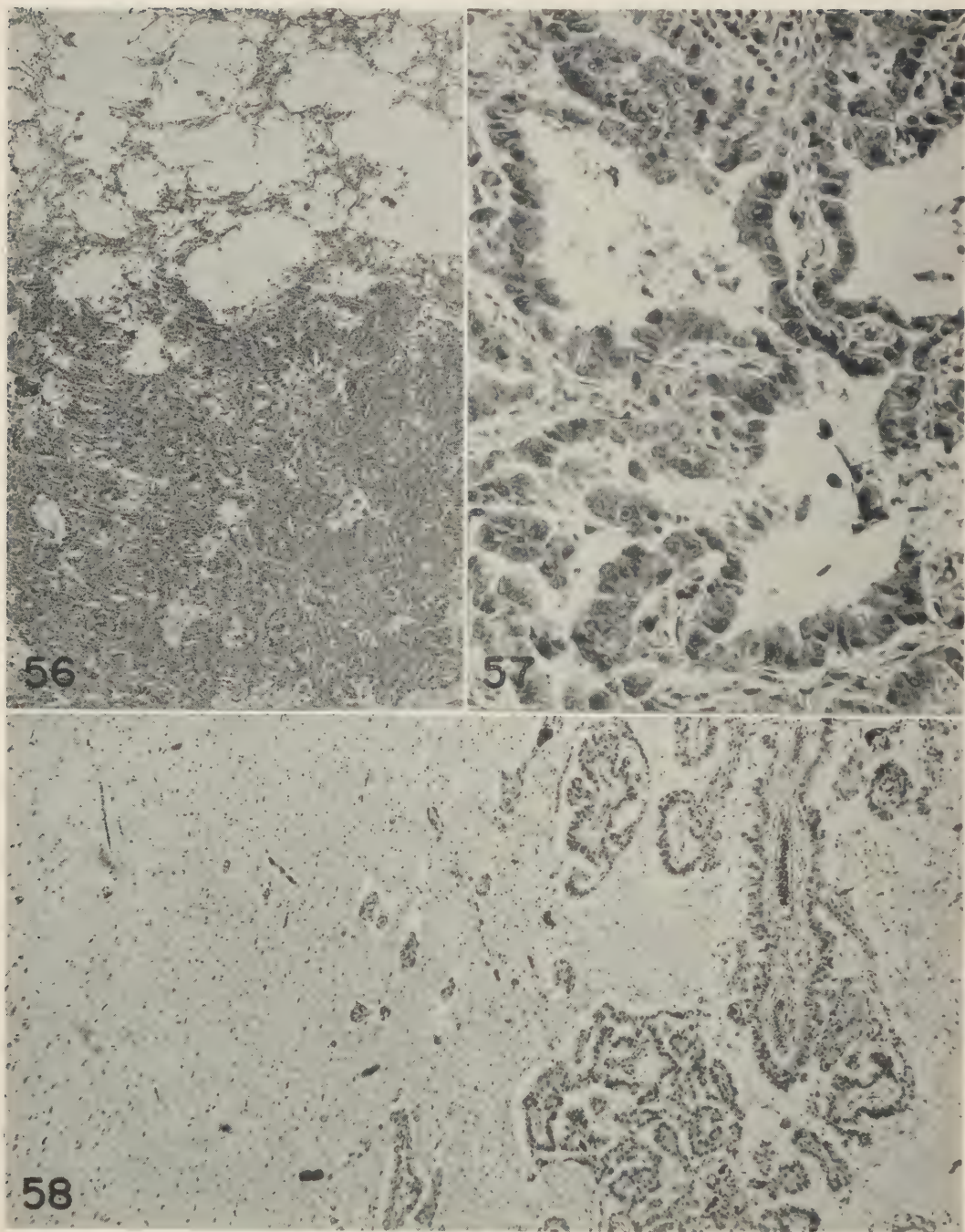


FIG. 56. Carcinoma of lung, primary tumor which metastasized to both eyes. $\times 30$. AIP Neg. 95910.

FIG. 57. Primary papillary adenocarcinoma of the lung, similar in appearance to the metastases in the eyes and other organs. $\times 230$. AIP Neg. 95908.

FIG. 58. Metastasis in the brain from the papillary adenocarcinoma of the lung. $\times 70$. AIP Neg. 95909.

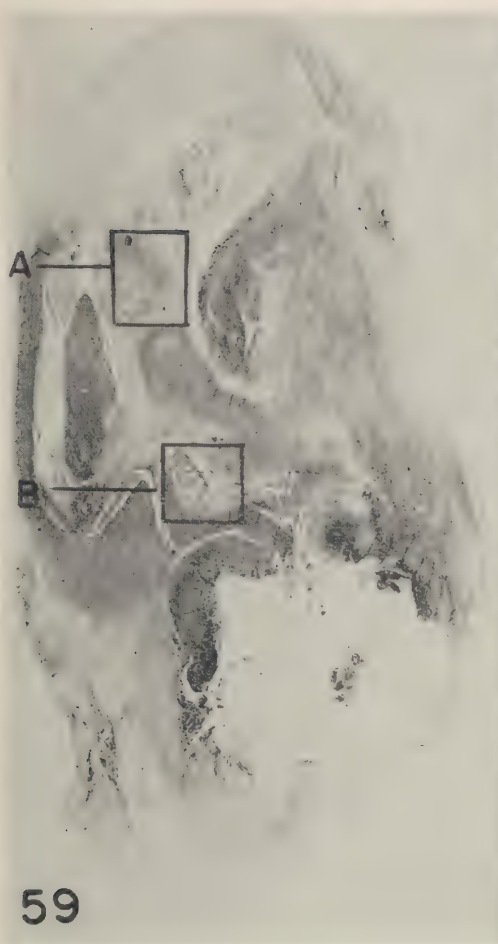


FIG. 59. Intra-ocular epithelial implants following penetrating wound. A, implant in the ciliary region. B, implant in the posterior segment near the site of a foreign body. $\times 5$. AIP Neg. 95860.

FIG. 60. Hyperplasia of an intra-ocular epithelial implant (Fig. 59B). $\times 60$. AIP Neg. 95897.

field for tumor implants.

Much has been written on the subject of intra-ocular implants following trauma and surgery (Perera²⁴) but this is the first time, so far as I know, that changes have been observed in them which might be interpreted as malignant.

VON HIPPEL'S HEMANGIOMATOSIS

The last growth of the series represents a malformation rather than a true tumor. It occurred in a 28 year old white soldier who, 2 years before the eye was enucleated, noticed a blurring of vision which increased rapidly in the last 5 months. On ophthalmoscopic examination a highly vascularized mass, about 3

disc diameters in size, was visualized projecting forward from the disc and retina, below. Roentgenograms revealed questionable lesions of the sella turcica and mediastinum. All other examinations were negative. Although a diagnosis of probable von Hippel's disease was given, the eye was enucleated because of the possibility of malignant neoplasm. The eye was opened in the vertical plane and a vascular mass measuring $4 \times 3 \times 2.5$ mm. was seen at the nerve head.

Microscopic examination revealed a mass involving the nerve head and adjacent retina with cystoid degeneration of the outer plexiform layer of the retina near the tumor (Fig. 63). Gliosis was present throughout most of

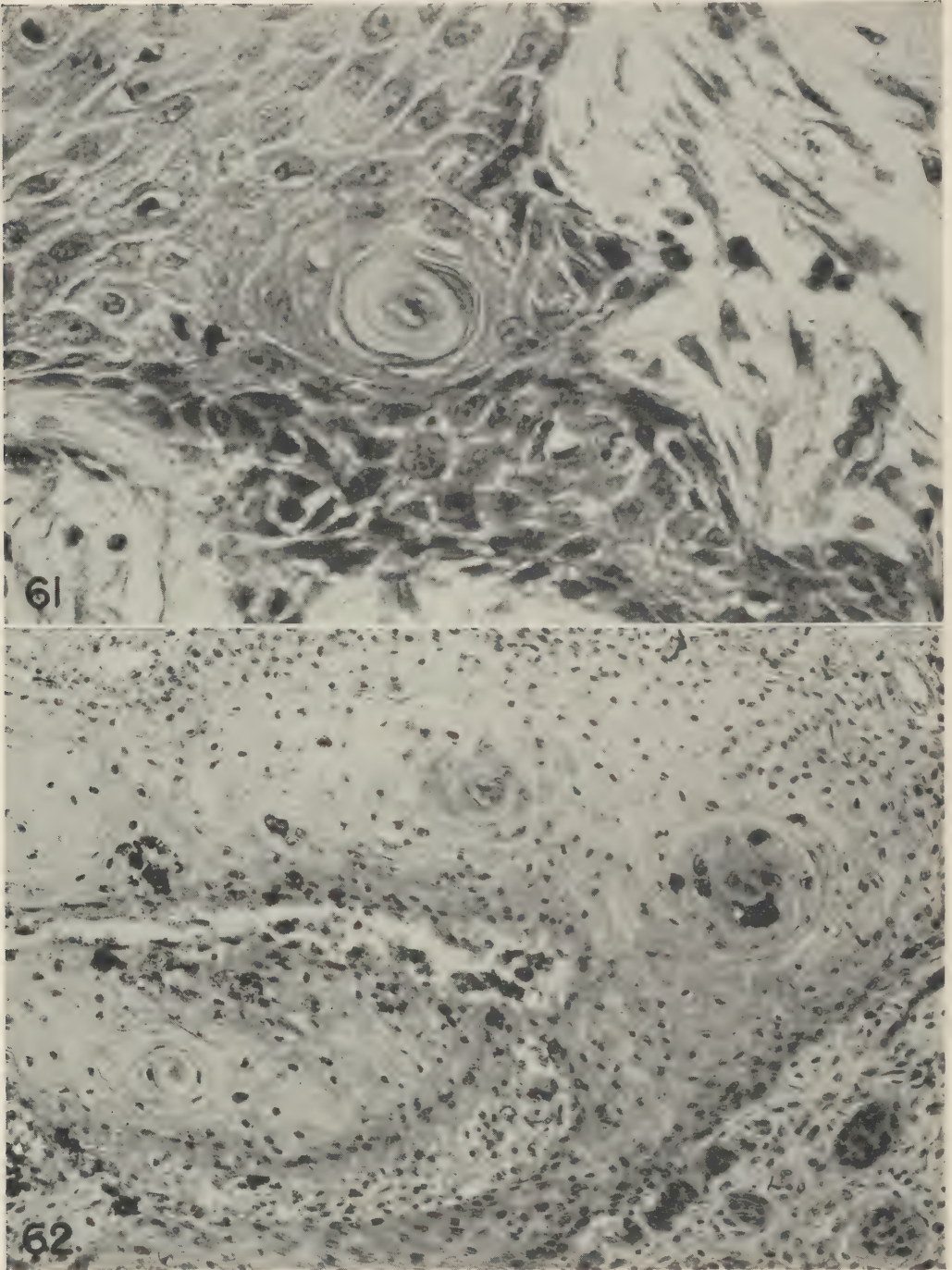
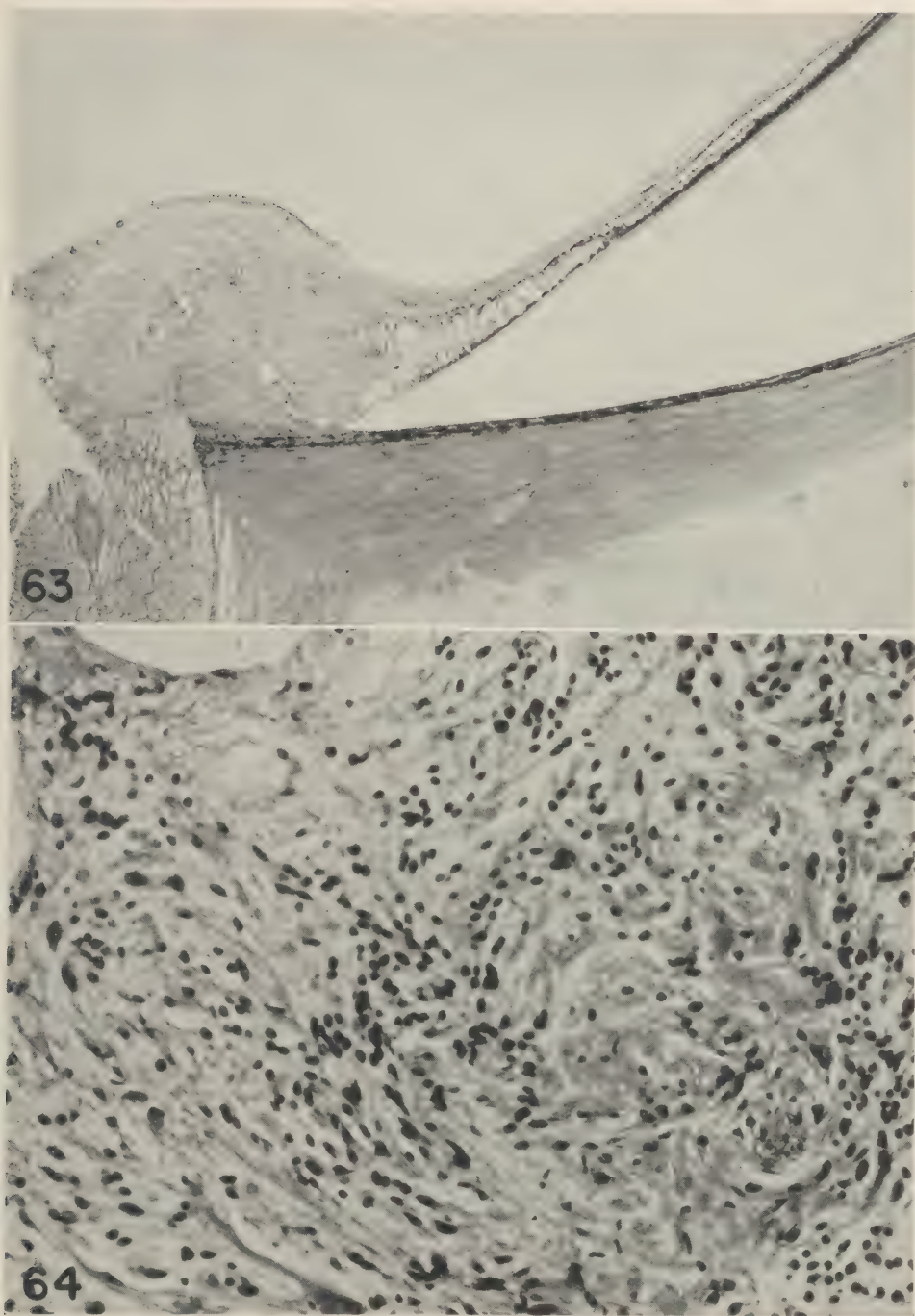


FIG. 61. Prickle cells with prominent intercellular bridges and an epithelial pearl in an intra-ocular implant (Fig. 59B). $\times 550$. AIP Neg. 95900.

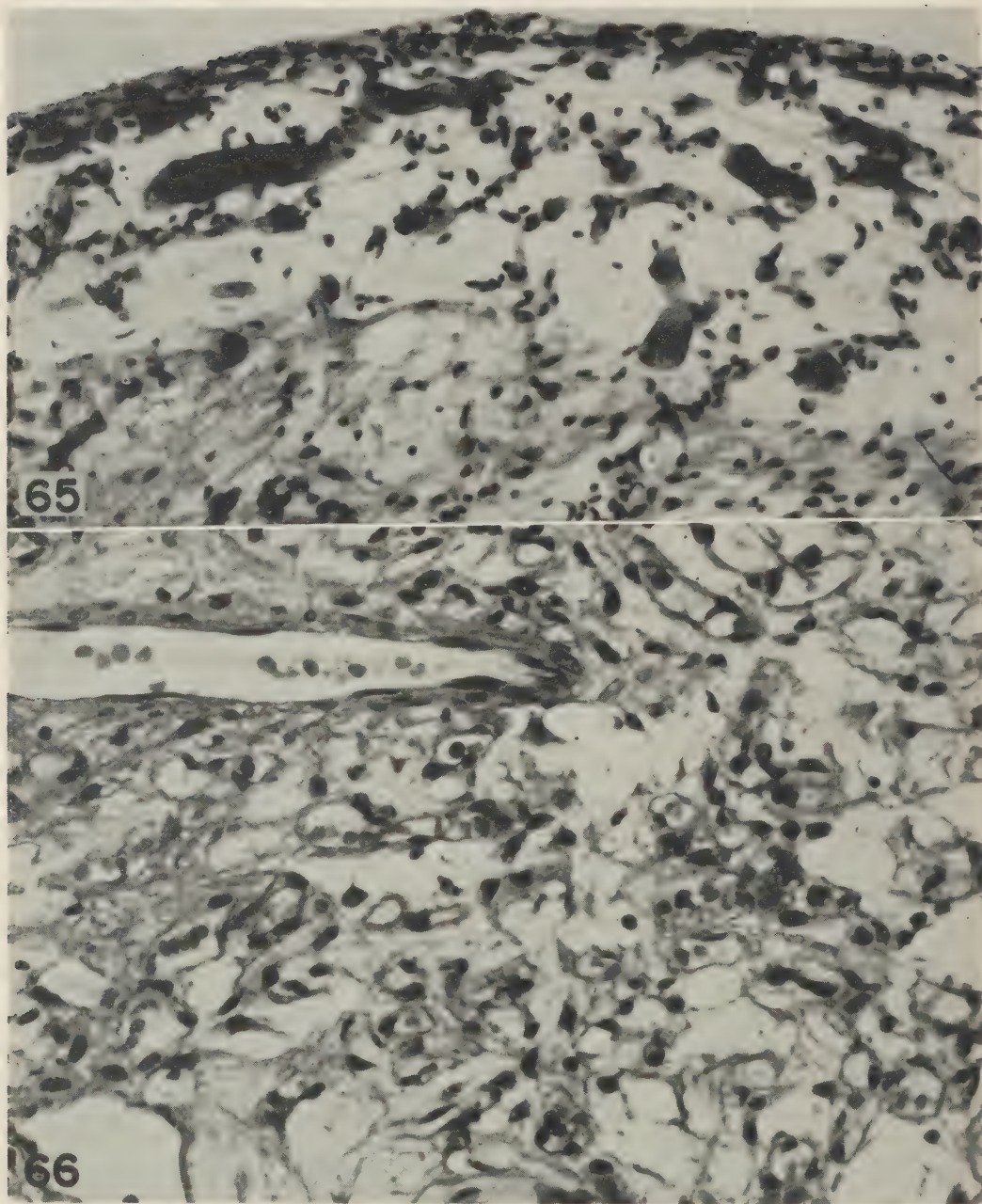
FIG. 62. Pearl formation in an epithelial implant (Fig. 59A). Nests of epithelial cells are seen beneath the large mass, suggesting invasion. $\times 200$. AIP Neg. 95898.



VON HIPPEL'S HEMANGIOMATOSIS

FIG. 63. Involvement of the nerve head and adjacent retina. Cystoid degeneration of the outer plexiform layer of the retina near the tumor. $\times 14$. AIP Neg. 95902.

FIG. 64. Glial proliferation in the tumor. $\times 250$. AIP Neg. 96222.



VON HIPPEL'S HEMANGIOMATOSIS

FIG. 65. Proliferated capillaries and glial cells in the superficial portion of the tumor. $\times 500$. AIP Neg. 96223.

FIG. 66. Thin-walled blood channels, some containing red blood cells, in the deep portion of the tumor. $\times 500$. AIP Neg. 95901.

the mass but was particularly marked at its periphery where it involved the retina (Fig. 64). Here the proliferated glial cells and their fibers were arranged in whorls and bundles. Elsewhere the vascular nature of the tumor was apparent. Proliferation of thin-walled blood vessels with intervening glial proliferation was present in the inner portion of the tumor (Fig. 65). In the deeper portion, numerous small channels usually lined by a single layer of endothelial cells frequently contained red blood cells (Fig. 66); occasionally better formed vessels were seen. Histologically the tumor was characteristic of hemangiogliomatosis or von Hippel's disease, and, with the history of possible lesions of the sella turcica and mediastinum, it must be considered as a probable component of Lindau's syndrome.

SUMMARY

Only 1.08 per cent of eyes enucleated from soldiers 18 to 38 years of age between Pearl Harbor and VJ Day and submitted to the Army Institute of Pathology contained intra-ocular neoplasms. These, however, included a variety of tumors both primary and metastatic. Represented in the group were: benign and malignant melanomas of the uveal tract; bilateral intra-ocular metastases from carcinoma of the lung and from malignant melanoma of the skin; malignant dyskeratosis in a traumatic intra-ocular epithelial implant, and von Hippel's disease. Malignant melanoma of the uveal tract was the most common tumor and benign melanoma was next in frequency. Those benign melanomas which occurred in the choroid were incidental findings in eyes enucleated following trauma. One was in an eye which had suffered a preinduction injury resulting in phthisis bulbi, but the other five, unless they had showed malignant change, would probably have gone unnoticed in civilian life.

Additional information concerning melanoma, relative to histologic malignancy and age incidence, indicate that the less malignant histologic types are more often found in tumors removed from patients less than 40 years of age than from those in the later decades. The

other growths were represented by single cases and may be looked upon as rare. Metastatic carcinoma of the choroid from the lung is relatively infrequent, particularly in this age group. The case of intra-ocular metastases of malignant melanoma is the eleventh to be reported. Von Hippel's angiomas, although a fairly large number of cases has been studied pathologically since the first was reported by Panas and Remy in 1879,²⁵ is not often seen clinically and less often comes to enucleation. In the case reported here, there was clinical evidence of Lindau's syndrome. No reference has been found in the literature to malignant dyskeratosis of an intra-ocular epithelial implant and it is believed that the condition is reported here for the first time.

It is inevitable that rare conditions should appear in such a large group subjected to compulsory physical examination and with readily available medical facilities. It is, however, surprising that under these circumstances the percentage of the more usual intra-ocular tumors should remain so low.

REFERENCES

- ¹ Reese, A. B.: Pigment freckles of the iris (benign melanomas): their significance in relation to malignant melanoma of the uvea. *Am. J. Ophth.* 27:217-226, 1944.
- ² Callender, G. R.: Malignant melanotic tumors of the eye: a study of histologic types in 111 cases. *Tr. Am. Acad. Ophth.* 131-142, 1931.
- ³ Callender, G. R., and Wilder, H. C.: Melanoma of the choroid; the prognostic significance of argyrophil fibers. *Am. J. Cancer.* 25:251-258, 1935.
- ⁴ Wilder, H. C., and Callender, G. R.: Malignant melanoma of the choroid: further studies on prognosis by histologic type and fiber content. *Am. J. Ophth.* 22:851-855, 1939.
- ⁵ Callender, G. R., Wilder, H. C., and Ash, J. E.: Five hundred melanomas of the choroid and ciliary body followed five years or longer. *Am. J. Ophth.* 25:926-967, 1942.
- ⁶ Wilder, H. C.: An improved technique for silver impregnation of reticulum fibers. *Am. J. Path.* 11:817-819, 1935.
- ⁷ Theobald, G. D.: Neurogenic origin of choroidal sarcoma. *Arch. Ophth.* 18:971-997, 1937.
- ⁸ Duke-Elder, W. S.: *Textbook of Ophthalmology.* The C. V. Mosby Co., St. Louis, Missouri. Vol. 3, 2446-2536, 1941.
- ⁹ Fuchs, E.: *Das Sarcom des Uvealtractus.* Wien, W. Braumüller, 1882.

¹⁰ Parsons, J. H.: *Pathology of the Eye*, London, Hodder and Stoughton. Vol. 2, pt. 2, p. 533, 1905.

¹¹ Brömser, G.: Ueber einen Fall von secundarem Melanom der Chorioidea. Berlin, G. Lange. Pt. 1, 45 pp., 1870.

¹² Schiess-Gemuseus and Roth, M.: Metastatisches Sarcom der Papille und angrenzenden Retina. Arch. f. Ophth. 25:177-192, 1879.

¹³ Pflüger, E.: Metastatisches Sarcom der Chorioidea. Arch. f. Augenh. 14:129-132, 1884-5.

¹⁴ Boente: Metastatische Melanoblastome in der Retina. Klin. Monatsbl. f. Augenh. 82:732-740, 1929.

¹⁵ Cordes, F. C., and Horner, W. D.: Metastatic melanoma of both eyes. Case Report. J.A.M.A. 95:655-658, 1930.

¹⁶ Corrado, A.: Sul sarcoma metastatico del corpociliare. Arch. d. Ophth. 38:508, Sept., 523, Oct., 1931.

¹⁷ Fry, W. E.: Metastatic sarcoma of the choroid. Am. J. Ophth. 9:248-255, 1933.

¹⁸ Uhler, E. M.: Metastatic malignant melanoma of

the retina. Am. J. Ophth. 23:158-162, 1940.

¹⁹ Adamük, V.: Ein Fall von metastatischen melanosarkomder Uvea. Zeitschr. f. Augenh. 21: 505-509, 1909.

²⁰ ten Doesschate, G.: Over metastatisch sarkom in het oog. Nederl. tijdschr. v. geneesk. 2:1432-1436, 1919.

²¹ Usher, C. H.: Cases of metastatic carcinoma of the choroid and iris. Brit. J. Ophth. 7:10-54, 1923.

²² Lucké, B., and Schlumberger, H.: Transplantation epitheliomas of the lip and mouth of catfish. J. Exper. Med. 74:397-408, 1941.

²³ Greene, H. S. N.: Participation of anterior chamber of eye in resistance phenomena related to tumor growth. Cancer Research. 2:669-674, 1942.

²⁴ Perera, C. A.: Epithelium in the anterior chamber of the eye after operation and injury. Am. J. Ophth. 21:605-617, 1938.

²⁵ Panas, F., and Remy, A.: Anatomie pathologique de l'oeil. Paris, V. Adrien Delahaye et C^{ie}, Libraires-Editeurs. 88, 1879.



THE OCCURRENCE AND ANATOMIC CHARACTERISTICS OF FATAL TUBERCULOSIS IN THE U. S. ARMY DURING WORLD WAR II*

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(With one chart)

DURING World War II, in the United States and its possessions, the enrollment, mobilization, and induction of great numbers of men, and the entrance into the military service of a large group of women made it possible, as never before, to obtain precise data on the incidence of tuberculosis in the general population, as well as on the occurrence and evolution of tuberculosis among Army personnel.

The attempt made during World War I to exclude men with manifest tuberculosis from the military service was only partially successful due to the great dependence on physical signs and the limited use of roentgenologic examination. Improvements in roentgenologic equipment and technique and the establishment of diagnostic standards since World War I, have made possible routine roentgenologic examination of large numbers of persons.

Although the number of fatal cases of tuberculosis received at the Army Institute of Pathology must not be construed as the true index of the mortality of the disease in the Army, comparison with preliminary official data of the Surgeon General's Office shows close agreement. In view of this fact and of the further consideration that the differences between the mortality from tuberculosis in World War II and in previous comparable periods are so great that they could not be appreciably affected by slight revisions in the data, it is believed appropriate to present the following comparisons.

A striking decline in mortality from tuberculosis has occurred between World Wars I and II in both the military and general populations of the United States. Table I and Figure 1 present the comparison between civilian and

Army experience by standard age groups at approximately the same time (1920 and 1940). It will be noted that because of the existence of hospital facilities in the Veterans Administration during World War II, it has been necessary to add to the figures of the Surgeon General's Office for World War II

TABLE I
AGE-SPECIFIC MORTALITY FROM TUBERCULOSIS IN
THE MILITARY AND CIVILIAN POPULATION,
WORLD WARS I AND II
(Deaths per 100,000)

Age in years	World War I*	Civilian Popula- tion 1920†	World War II‡	Civilian Popula- tion 1940†
18-19	43.8	107.5	4.2	26.0
20-24	60.4	151.0	7.3	40.4
25-29	67.6	162.6	5.8	51.0
30-34	87.4	163.7	6.1	59.8
35-39	122.2	170.0	9.4	70.0
40-44	97.7	172.0	13.4	78.2
45 plus	89.6	174.0	17.1	86.0
Mean all ages§	65.9	151.4	6.7	47.7

* Med. Dept. of the U. S. Army in the World War, Vol. XV.

† Tuberculosis in the United States, prepared by National Tuberculosis Association and U. S. Public Health Service, 1943.

‡ Estimated from Army Institute of Pathology data and from Veterans' Administration for period from Dec. 7, 1941 to Dec. 1945, inclusive.

§ Civilian mean rate for all ages standardized by use of respective Army age distribution for June 30, 1945, based on A.G.O. sample data applied to total strength from Dec. 1941 to Dec. 1945.

those service-connected deaths from tuberculosis of veterans of this war in hospitals of the Veteran's Administration.

Average annual mortality from tuberculosis, to date, in the Army of World War II has

* From the Army Institute of Pathology, Washington, D.C.

TUBERCULOSIS MORTALITY (all forms)

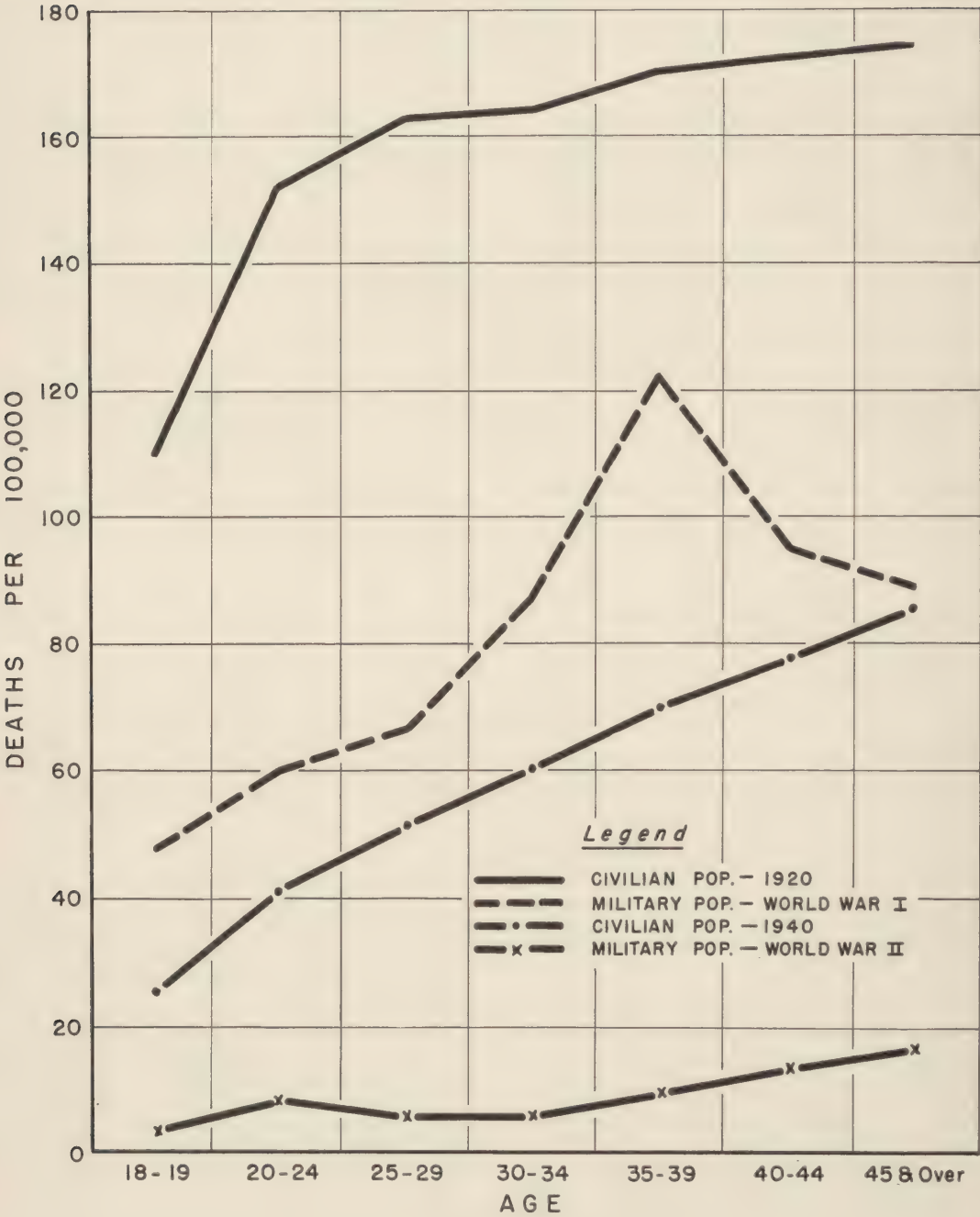


FIG. 1

been approximately but one-seventh of that of the civilian population in the year 1940, the rate among Army personnel being about 7 per 100,000, as compared to the civilian rate of 48, standardized with respect to the Army age distribution. In addition, between World Wars I and II the mortality rates of tuberculosis in the Army population dropped 90 per cent, while that in the civilian popula-

lated to the occurrence of fatal tuberculosis in United States Army personnel and with the distribution and character of the lesions. It is based on an analysis of the available clinical records and autopsy protocols of 579 males and 2 females who died in the United States or abroad between December 7, 1941 and December 1945, inclusive, in which the primary cause of death was tuberculosis. This

TABLE 2
NUMBER OF DEATHS FROM TUBERCULOSIS IN THE U. S. ARMY BY
YEAR OF OCCURRENCE AND RACE

Race	Year of Death				Total	Percent by Race
	1942	1943	1944	1945		
White	37	81	95	84	297*	51.1
Negro	30	82	87	53	252	43.4
Indian	3	3	3	3	12	2.7
Filipino	2	2	1	4	9	1.5
Hawaiian	1	0	0	0	1	0.1
Puerto Rican	0	0	2	2	4	0.6
Chinese	0	1	1	1	3	0.5
Japanese	1	0	2	0	3	0.5
Total	74	169	191	147	581	

* Two females included.

tion of the same age composition fell 69 per cent. Preinduction roentgenologic examination carried out in World War II is probably the most significant factor responsible for the extremely low mortality from tuberculosis in the Army during this war as compared with that of the civilian population and of the army in World War I.

The pre-induction roentgenologic examination of the chest of large numbers of persons from the general population has proved of great value in the control of tuberculosis, since numerous previously undiagnosed cases of this disease have been detected and referred for observation and treatment. Dempsey¹ estimated in 1943 that within that year approximately 12,000,000 persons in the general population would have been examined roentgenologically and it was estimated that about 25,000 of those examined would require hospitalization for tuberculosis.

The present study deals with factors re-

lated to the occurrence of fatal tuberculosis in United States Army personnel and with the distribution and character of the lesions. It is based on an analysis of the available clinical records and autopsy protocols of 579 males and 2 females who died in the United States or abroad between December 7, 1941 and December 1945, inclusive, in which the primary cause of death was tuberculosis. This study does not include the 805 service-connected deaths from tuberculosis of those members of the Army who died in the hospitals of the Veterans' Administration from July 1942 to July 1945. The number of deaths from tuberculosis exclusively in Army hospitals is shown in reference to year and race in Table 2.

EFFECT OF RACE, AGE, AND LENGTH OF SERVICE ON OCCURRENCE OF TUBERCULOSIS IN THE ARMY

The interpretation of many studies dealing with variations in the morbidity, the evolution, and the mortality from tuberculosis among racial groups is complicated by economic and environmental factors which differ widely among these groups. Experimental studies disclose wide variations in the resistance of laboratory animals to infection with *M. tuberculosis*. Wright and Lewis² showed that in five families of guinea pigs inbred by

brother and sister mating over a long period of time there existed marked differences in the resistance to infection by a virulent strain of *M. tuberculosis*. Lewis and Loomis³ using the same families of guinea pigs found that the local lesions following the intracutaneous injection of a virulent strain of *M. tuberculosis* was unlike in the different families. In the most resistant family the ulcer tended to heal and did not involve, grossly, the regional lymph nodes. In the least resistant family not only did the ulcer fail to heal but the regional nodes became swollen, matted, and ulcerated. Kuster and Kroning⁴ have confirmed the observations of Wright and Lewis² as to the variation in resistance of different inbred families of guinea pigs to tuberculosis and have concluded that resistance is a hereditary factor. Lurie⁵ exposed six inbred families of rabbits to respiratory tuberculous infection. He found that in the most resistant family the pulmonary lesions tended to be localized and ulcerative in character, resembling those of reinfection in man, and that there were no gross lesions in the regional tracheobronchial nodes. On the other hand, in the most susceptible family the lesions became confluent giving rise to a tuberculous bronchopneumonia with extensive involvement of the draining tracheobronchial nodes and a tendency to hematogenous spread. Aronson, Parr and Saylor⁶ have noted marked variation in the local ulceration following the intracutaneous injection of a viable, attenuated, bovine type of *M. tuberculosis* (Calmette-Guerin strain) in Indian children. In one group of children and young adults the resulting ulceration tended to be saucerlike and punched out, with the surface covered with healthy granulations, while in another group the ulcer had a small crater-like opening with undermined edges, typical of a tuberculous ulcer, which healed slowly.

It has long been recognized that definite differences exist in the incidence, evolution, mortality, and anatomic characteristics of tuberculosis in the white and the colored. Thus the death rates per 100,000 from tuberculosis in the United States for 1940 was 36.5 for the white race and 127.6 for the colored.

Studies of Israel and Payne⁷ indicate that the high rate and the rapid course of tuberculosis among the colored is to be attributed to the fact that the tuberculous lesion is more acute and rapid in its evolution. The precise studies of Opie,⁸ and the investigations of Everett,⁹ Pinner and Kasper¹⁰ indicate that the anatomic character of the tuberculous process in the colored is different from that in the white. The interpretation of data on resistance to tuberculosis among different racial groups is complicated by economic and environmental factors in civilian life. In the Army the influence of these factors is generally absent, since for all military personnel patterns of housing, clothing, feeding, and remuneration are uniform while the duties incidental to military life are not affected by racial lines. As a result, a study of the occurrence and evolution of tuberculosis in the Army is of great significance in evaluating racial susceptibility and resistance. Despite the uniform social and economic conditions Table 2 shows that Negroes, who make up approximately 10 per cent of the Army population, contribute 43.4 per cent of the total deaths from tuberculosis. Among the American Indians who numbered approximately 25,000, or 0.3 per cent of the Army population, there occurred ten, or 2.7 per cent, of all deaths from tuberculosis. These figures suggest that the high rate of tuberculosis among Negroes and Indians may be due in part to an innate lower degree of resistance to the disease rather than to poor economic and environmental factors.

The mechanism involved in the selective role that age plays in the development of tuberculosis and the resulting mortality is not clearly understood. Thus for the year 1940¹¹ in the general white population the relatively high rate of tuberculosis among those under 5 years of age was followed by a greatly reduced rate for the age group of 5 to 14 years. A sharp rise in the rate for the 15-to-19-year and the 20-to-24-year groups was succeeded by a more gradual increase which reached its peak in the 65-to-74-year group. Among the colored a sharp rise occurred in the 10-to-14

and the 15-to-19-year groups, reaching the peak of mortality in the 20-to-24-year group. This predilection for certain age periods in different races cannot be explained solely on the basis of exposure to tuberculosis and is probably modified by other factors. The distribution by age and racial groups of fatal tuberculosis in Army hospitals during World War II is presented in Table 3. The per-

centage of deaths observed in the various age groups is compared with the per cent distribution of these age groups in the Army as a whole. The transfer of large numbers of men from their homes to the crowded barracks of Army camps and the change from civilian occupation to duties involving physical stress and exposure might lead to an increase in tuberculosis. Many men came from rural areas where they had more often escaped tuberculous infection. The relationship between the length of service and the occurrence of fatal tuberculosis by

TABLE 3
MORTALITY FROM TUBERCULOSIS BY AGE AND RACE*

Age in years	White		Negro		All races		Percentage distribution in Army
	No.	Per cent	No.	Per cent	No.	Per cent	
18-19	25	7.5	11	4.4	36	6.2	9.1
20-24	125	38.3	116	46.4	241	41.7	37.6
25-29	87	26.5	63	25.1	150	26.0	29.8
30-34	54	16.5	30	11.9	84	14.4	16.2
35-39	23	7.0	26	10.3	49	8.5	5.8
40 plus	14	4.2	5	1.9	19	3.2	1.5
Total	328	100.0	251	100.0	579	100.0	100.0

* Based on Army age distribution for June 1945 as shown in A.G.O. sample data and representative of age distribution throughout period of World War II.

centage of deaths observed in the various age groups is compared with the per cent distribution of these age groups in the Army as a whole.

It will be observed from Table 3, that the largest percentage of deaths occurred among those in the age group of 20 to 24 which includes the largest percentage of soldiers, and that there was no sharp racial variation in the percentage of deaths at different ages. Comparison of the distribution of the age at which deaths from tuberculosis occurs with the age distribution of the Army as a whole indicates that mortality from tuberculosis increases with age, particularly in men above 34 when the rate becomes almost 50 per cent greater than that in men below this age. It should be noted, however, that men above 35 in the Army are much less representative of all men in that age group than are those in the younger groups.

The relationship of the length of active Army service to the occurrence of fatal tuberculosis was analyzed. The possibility exists that

year and race is presented in Table 4.

It will be noted from Table 4 that the percentage of deaths from tuberculosis, all races, was largest during 1942 and 1943 among those who had the shortest length of service. In 1944 and 1945 the peak of deaths was among those who had a year or more of Army service. These differences might be explained on the basis of the rate of expansion of the Army. In 1942 approximately 3,500,000 were inducted and in 1943 approximately 2,200,000 were inducted, while in 1944 and 1945 only 600,000 and 150,000 respectively entered the Army. While this is the most likely explanation for these differences, it is also possible that the larger number of deaths in the early days of the war may have been due to the induction of a number of men not examined roentgenologically, who may have had a tuberculous process which gave rise neither to subjective symptoms nor to physical signs. The high death rate of the group who had served but a short time in the Army may be

TABLE 4
MORTALITY FROM TUBERCULOSIS IN RELATION TO ACTIVE ARMY SERVICE, ALL RACES
(per cent distribution)

Months of Active Service	Year				Total
	1942	1943	1944	1945	
0-6	42.9	43.6	13.1	6.1	23.9
7-12	18.6	24.2	17.0	12.1	18.1
13-18	25.7	10.7	24.4	8.3	16.7
19-24	8.6	8.7	19.3	22.7	15.8
25-30	0.0	7.4	13.6	14.4	10.2
31-36	0.0	2.0	5.7	22.0	7.9
37-42	0.0	2.0	6.8	6.8	2.8
43-48	4.2	1.4	0.0	7.6	4.5
Total	100.0	100.0	100.0	100.0	100.0
Deaths	70	149	176	132	527

explained in still other ways. Possibly persons who had escaped previous tuberculous infection were overcome by their primary infection or others who had little resistance to tuberculous infection may have been infected and had rapidly progressive tuberculosis.

Table 5 compares the frequency of fatal tuberculosis among white and Negro with reference to length of active Army service. It is clear that there was no significant trend to indicate that members of either group contracted tuberculosis relatively earlier or later in their period of service.

It is possible that morbidity and mortality from tuberculosis may be influenced not only by the length of service in the Army but also

by the place of service. Thus, service in foreign lands, especially during and immediately following war, might result in heightened susceptibility due to fatigue, or increased exposure resulting from unhygienic surroundings, from billets in heavily infected communities and homes, or from intimate contact with tuberculous civilians, whose number increases rapidly with privation. The per cent distribution of deaths from tuberculosis in relation to foreign or domestic service by race and in relation to the distribution of troops is presented in Table 6. It will be observed from this table that during 1942 and 1943 the percentage of deaths from tuberculosis paralleled closely the distribution of Army personnel;

TABLE 5
MORTALITY FROM TUBERCULOSIS IN RELATION TO RACE AND LENGTH
OF ACTIVE ARMY SERVICE

Months of Service	White		Negro		Total all Races	
	Number	Per cent	Number	Per cent	Number	Per cent
0-6	65	22.4	61	25.9	126	23.9
7-12	46	15.8	49	20.7	95	18.1
13-18	52	17.9	36	15.3	88	16.7
19-24	39	13.4	44	18.7	83	15.8
25-30	35	12.1	19	8.1	54	10.2
31-36	27	9.2	15	6.3	42	7.9
37-42	18	6.2	6	2.5	24	2.8
43-48	9	3.8	6	2.5	15	4.5
Total	291	100.0	236	100.0	527	100.0

TABLE 6
MORTALITY FROM TUBERCULOSIS IN U. S. ARMY IN RELATION TO FOREIGN
OR DOMESTIC SERVICE BY AGE AND RACE

	White		Negro		All Races		Distribution of Army	
	Foreign	Domestic	Foreign	Domestic	Foreign	Domestic	Foreign	Domestic
Year	Per cent	Per cent	Per cent	Per cent	Per cent	Per cent	Per cent	Per cent
1942	13.7	86.3	10.0	90.0	12.2	87.8	18	82
1943	24.2	75.8	18.3	81.7	21.3	78.7	25	75
1944	61.5	38.5	61.0	39.0	61.3	38.7	50	50
1945	86.3	13.7	73.5	26.5	81.5	18.5	62	38

however, during 1944 and 1945 the percentage was conspicuously higher among those serving in foreign lands. To a certain degree this rise is to be attributed to tuberculosis among Americans and Filipinos who were prisoners in the infamous enemy prison camps. The relative differences in the percentages for racial groups were constant in all theaters, except in 1945, when the white group overseas showed a sharp increase, probably resulting from this high incidence among released prisoners of war.

DURATION OF TUBERCULOUS PROCESS

Accumulated evidence indicates that the course of the tuberculous process is more rapid

among the colored than among the white. Rogers¹² found that the mean duration of tuberculosis was 13 months for colored and 18 months for white. Opie¹³ observed that among Negroes living in Jamaica, B. W. I., tuberculosis for those between 15 and 30 years averaged 9 months, while for a group of white patients of comparable age in Philadelphia it averaged 28 months. Pinner and Kasper¹⁰ found that tuberculosis averaged 995 days for 96 white and 324 days for 47 colored. It has been assumed that the shorter duration of tuberculosis in the colored is to be attributed to failure to seek medical care until the disease has progressed. Israel and Payne,⁷ however, found that the relatively

TABLE 7
DURATION OF SYMPTOMS, BY MONTH, FOR WHITE AND NEGRO

Months	Total White		Total Negro		Total All Races	
	No.	Per cent	No.	Per cent	No.	Per cent
0-1	36	11.3	24	9.8	60	10.7
1-2	46	14.4	23	9.4	69	12.2
2-3	37	11.6	21	8.6	58	10.3
3-4	25	7.8	23	9.4	48	8.5
4-5	27	8.5	21	8.6	48	8.5
5-6	30	9.4	26	10.5	56	9.9
6-7	24	7.5	31	12.7	55	9.7
7-8	15	4.7	18	7.3	33	5.8
8-9	11	3.4	11	4.5	22	3.9
9-10	9	2.8	12	4.9	21	3.7
10-11	12	3.7	7	2.8	19	3.3
11-12	8	2.5	3	1.2	11	1.9
12 and over	39	12.2	25	10.2	64	11.2
Total	319	100.0	245	100.0	564	100.0

short course of the disease in the Negro was due not to the neglect of early symptoms but to the acute evolution of the tuberculous lesion, which was frequently exudative in character. Their cases were selective insofar as they were of a more or less chronic nature, but the autopsy material forming the basis for the

considerably from the data previously cited, in which the course of tuberculosis was appreciably longer in the white. The principal reason for this discrepancy probably lies in the fact that the cases studied in this survey are acute cases, while those in the literature were primarily chronic cases of tuberculosis.

TABLE 8
DURATION OF SYMPTOMS IN RELATION TO TUBERCULOUS MENINGITIS*

Duration in Months	White		Negro		All Races
	Total deaths from Tuberculosis	Deaths from Tuberculous Meningitis	Total deaths from Tuberculosis	Deaths from Tuberculous Meningitis	Deaths from Tuberculous Meningitis
	Number	Per cent of total	Number	Per cent of total	Per cent of total
0-2 incl.	111	63.9	58	42.6	56.1
3-5	79	41.5	69	20.0	31.6
6-8	46	36.0	57	25.0	30.0
9-11	27	34.5	25	9.1	23.5
12 and over	39	17.9	22	12.0	15.6
Over all per cent		45.5		25.7	36.9
Average Duration in months Tuberculous Meningitis		4.2		4.5	4.3
Average Duration in months Tuberculosis without Meningitis		7.0		6.6	6.8
Average Duration in months All cases		5.7		6.1	5.8

* Including tuberculous cases in which meningitis was a terminal complication.

present study is also selective since it represents the more acute cases in Army hospitals.

The duration of tuberculosis as determined from subjective symptoms, confirmed by roentgenologic or bacteriologic examination or both, was investigated. The distribution of the duration of the disease in months for 319 white and 245 colored soldiers is presented in Table 7.

This analysis indicates that, in general, the duration of symptoms was not conspicuously different for any or all the years among the white and colored groups, the average for the white being 5.7 months, while that for the Negro was 6.1 months. This result differs

One of the more frequent forms of acute tuberculosis observed in this study is tuberculous meningitis. Forty-five and five tenths per cent of the cases of tuberculosis among the white soldiers took this form, whereas it occurred in only 25.7 per cent of the Negro patients. In addition, it was found that the average duration of tuberculous meningitis was 4.2 months in the white and 4.6 months in the Negroes, which is appreciably below the average duration of 7.0 and 6.6 months respectively for tuberculosis without meningitis. The relatively higher proportion of tuberculous meningitis among the white patients operates to reduce the average duration of

symptoms in that group absolutely, and also relatively to that of the Negroes. Table 8 presents the data suggesting this view.

PATHOLOGIC ANATOMY

The pathologic material on which this study is based is from autopsies performed in Army

The tabulation presented in Table 9 indicates that in this series of cases no outstanding racial differences were noted in the frequency with which tuberculous lesions appeared in any of the organs. It will be seen, however, that brain, meninges, seminal vesicles and prostate were more often involved in the white, and

TABLE 9
OCCURRENCE OF TUBERCULOSIS IN DIFFERENT ORGANS BY RACE

Organs	White		Negro		All Races	
	No.	Per cent	No.	Per cent	No.	Per cent
Lungs	305	92.0	233	92.1	538	92.5
Tracheobronchial nodes	274	83.4	215	85.5	489	84.3
Brain	45	13.7	25	9.9	70	12.1
Meninges	147	44.8	65	25.8	212	36.3
Intestine	122	37.2	83	33.0	205	35.3
Peritoneum	45	13.7	51	20.2	96	16.5
Liver	224	68.2	158	62.5	382	65.8
Pancreas	24	7.3	21	8.3	45	7.7
Stomach	2	0.6	2	0.8	4	0.7
Heart	4	1.2	4	1.6	8	1.4
Pericardium	5	1.5	7	2.8	12	2.1
Kidneys	133	40.4	96	38.1	229	39.4
Ureter	6	1.8	1	0.4	7	1.2
Urinary bladder	10	3.2	4	1.6	14	2.4
Seminal vesicle	32	9.7	8	3.2	40	6.9
Prostate	69	21.0	22	8.3	90	15.5
Epididymis	14	4.2	10	3.9	24	4.1
Testes	13	3.9	8	3.2	21	3.6
Spleen	228	69.2	158	62.5	386	66.4
Adrenal	93	28.4	55	21.8	147	25.3
Thyroid	13	3.9	10	3.9	23	3.9
Vertebrae	9	2.7	22	8.7	31	5.3
Ear	3	0.9	2	0.8	5	0.8
Eye	2	0.6	0	—	2	0.3
Ribs	1	0.3	1	0.4	2	0.3

hospitals in cases of death from tuberculosis. It is necessarily incomplete because of the transfer of the more chronic cases to hospitals of the Veterans Administration, nor has it uniformity since the autopsies were performed by a number of prosectors whose interests, observations, and descriptions varied. The protocols have been analyzed to determine the distribution and the nature of the anatomic lesions. The frequency with which tuberculous processes were found in the various organs of the 329 white and 252 colored soldiers is presented in Table 9.

hilar nodes, peritoneum and vertebrae in the colored.

The studies of Opie,⁸ Everett,⁹ and of Pinner and Kasper¹⁰ indicate that the pulmonary lesions of tuberculosis in the Negro differ in their anatomic characteristics from those observed among the white. A composite description of the differences, according to the authors mentioned, indicates that in the Negro the tuberculous pneumonic lesion is less apt to involve the apex, tends to be exudative and ulcerative, while fibrosis is rare. The infection is usually spread by lymphogen-

ous and hematogenous routes and produces extensive involvement and massive caseation of the draining tracheobronchial nodes. In the white, on the other hand, the apex is more frequently involved and the formation of cavities is usual. There is a greater tendency toward localization and fibroconnective tissue formation. Spread of the tuberculous process by lymphogenous or hematogenous routes is less frequent than in the Negro, and the draining tracheobronchial nodes are more apt to undergo fibrosis and calcification.

RESPIRATORY SYSTEM

The distribution and character of the pulmonary lesions and their relation to associated

and confluent. In only a few instances did the prosectors report massive involvement of the hilar nodes among the colored.

The character of the draining tracheobronchial nodes was noted in 274 white and 215 colored. In 50, or 18.3 per cent, of the white and in 21, or 9.8 per cent, of the colored the draining nodes were calcified or fibrous. In 36, or 13 per cent, of the white and in 13, or 6 per cent, of the colored the nodes showed no gross lesions of tuberculosis.

In one instance miliary coccidioidomycosis was also present in a white male age 30, who reacted to both coccidioidin and tuberculin in dilutions of 1 to 100 and 1 to 1000, respectively, and in whose sputum both acid-fast

TABLE 10
OCCURRENCE OF PULMONARY AND ASSOCIATED TUBERCULOUS
LESIONS IN WHITE AND NEGRO

Lung and associated organ	White		Negro		All Races	
	No.	Per cent	No.	Per cent	No.	Per cent
Lung only	26	8.5	30	12.9	56	10.4
Miliary generalized	230	75.0	178	76.0	408	75.6
Meninges and brain	22	7.2	5	2.1	27	5.0
Gastro-intestinal	13	4.2	9	3.9	22	4.0
Liver	8	2.6	0	—	8	1.5
Peritoneum	0	—	3	1.3	3	0.5
Spleen	4	1.3	5	2.1	9	1.7
Vertebrae	2	0.6	3	1.3	5	0.9

tuberculous processes, as well as the characteristics of the draining regional tracheobronchial nodes, were studied in 306 white and 233 colored persons. The occurrence of pulmonary and associated lesions is presented in Table 10.

When the pathologic characteristics of the pulmonary lesions in the white and colored were compared, cavities were found in the lungs of 86.6 per cent of the white and 78.5 per cent of the colored, while generalized miliary tuberculosis (Table 10) was equally frequent in both races. Evidence of healed primary tuberculosis, as indicated by fibrous scars or calcified pulmonary nodules or both, was noted in 43, or 14.1 per cent, of the white and in 20, or 8.5 per cent, of the colored. In general, the tuberculous pneumonic lesions among the colored were more often ulcerative

bacilli and the spore form of *C. immitis* were found. From the cavity of the upper lobe, right lung, and from the pulmonary nodules, spores of *C. immitis* were demonstrated, while in the caseous material, acid-fast bacilli were noted. In the miliary lesions of the spleen, liver, and kidneys spores of *C. immitis* were found but no acid-fast bacilli.

In a white male aged 26 an extensive bilateral adenocarcinoma of the lung was associated with extensive tuberculous cavitation. Acid-fast bacilli in large numbers were found in the cavity, and the tracheobronchial nodes showed evidence of tuberculosis.

BRAIN AND MENINGES

Tuberculosis of the meninges, brain, or both was noted in 154, or 47 per cent, of the white

and in 70, or 28.2 per cent, of the colored. The process was primary in 9.7 per cent of the colored and in 7.1 per cent of the white, while it was associated with a generalized miliary tuberculosis of other organs in 79.5 per cent of the white and in 81.5 per cent of the colored. There was an associated involvement of the lung but of no other organ in 9.7 per cent of the white and 7.1 per cent of the colored, while in both racial groups the adrenal only was involved along with the meninges in 1 white and in 1 colored person. Meningitis was associated with tuberculous spondylitis in 1 white and 2 colored persons.

The meningitis was manifested by varying amounts of exudate, most marked at the base of the brain, extending through the pia-arachnoid. Definite tubercles, occasionally observed, were located either at the base of the brain or along the vessels. They did not differ from the usual tubercle except caseation was infrequent and slight. The vessel walls were often necrotic while the exudate consisted of large numbers of mononuclear cells and varying numbers of acid-fast bacteria. The paucity of definite tubercles in the meninges and the brain was probably due to the rapid course of the disease.

Tuberculomas of the brain were reported as occurring in 8 white persons and in 3 colored. It is probable that more would have been found had a particular search been made for them.

GASTRO-INTESTINAL TRACT

Tuberculous lesions of the gastro-intestinal tract differed neither in frequency nor character in relation to racial factors, except that tuberculous peritonitis was noted somewhat more often among the colored. The tuberculous process manifested itself by ulceration or lymphoid proliferation of the follicles in the submucosa and less frequently by ulceration or diffuse infiltration of the other layers of the intestine. Tuberculous peritonitis was associated with extensive involvement of the serosa of the intestines which at times penetrated the muscularis. The tuberculous process also affected the capsule of the liver and spleen,

although the parenchyma of the organs was relatively free of tubercles. Tuberculosis of the intestinal tract was most frequently noted in the ileum, cecum, colon and appendix. Tuberculous ulcers were present in the gastric submucosa of 2 white and 2 colored persons. The mesenteric nodes showed extensive caseation in most instances but calcification was infrequent. Tuberculosis of the pancreas occurred only as a part of generalized miliary tuberculosis. The lesions in the pancreas were usually discrete, small, and few in number.

The liver was tuberculous in 68 per cent of the white and 62 per cent of the colored, the extent and character of the lesions varying within wide limits, ranging from lymphoid proliferation to fibrosis, and occasionally to calcification.

HEART AND PERICARDIUM

Tuberculosis of the myocardium was observed in 4 white and 4 colored, all with generalized miliary tuberculosis. The tubercles were few, focal and miliary in character and showed little tendency to fibrosis. In 5 white and 7 colored the pericardium showed extensive caseonodose lesions, associated with other similar ones in the contiguous pleura.

GENITO-URINARY TRACT

In both white and colored, renal tuberculosis was found to be associated in every instance with generalized miliary involvement of other organs. There were 133 cases of renal tuberculosis among the white; in 91 miliary tubercles were present in the kidney and in 42 the tuberculous process was conglomerate and extensive, destroying large areas of the kidney. Miliary tubercles were noted in 75 of 96 cases among the colored while in the remaining 21 the lesions tended to be conglomerate and extensive. The lesions in the ureter and bladder were located in the mucosa and submucosa. At times the process was diffuse, especially in the urinary bladder. Tuberculosis of the prostate and seminal vesicle in both white and colored was associated with generalized miliary tuberculosis in all cases but one. This exceptional case was

that of a white soldier in whom the prostatic lesion was associated with tuberculous meningitis. The tuberculous process in the prostate was extensive, having destroyed the greater part of the gland in 61 of the 69 cases noted among white soldiers, while in 8 the lesions were miliary in character. Of the 22 cases among the colored, extensive destruction of the prostate was noted in 14 and miliary lesions in the remaining 8.

The extensive, destructive tuberculous lesions in the kidney, prostate, seminal vesicle, and testes are of interest and have been noted by other observers. The mechanism underlying the selective and extensive destruction of certain organs, especially those of the genitourinary tract and the adrenal, is not clearly understood.

SPLEEN

Tuberculosis of the spleen manifested itself, in most instances, by miliary tubercles in varying stages of development, and occasionally by conglomerate tubercles. Fibrosed tubercles were noted in 8 cases, calcified nodules in 1, and amyloid degeneration in 2 among the white. In general, among the colored there was a greater tendency for the tubercles to caseate and to become conglomerate. Calcified nodules in the spleen were observed in 5 instances, amyloid degeneration in 1, and fibrotic tubercles in 1.

ADRENAL

In the white the adrenal was involved in 93 cases. In 53 the tuberculous lesions were miliary and varied widely in number and stage of development. In 40 the adrenal showed large conglomerate tubercles which, in some cases, had destroyed the greater part of the organ. In one case of tuberculous meningitis the adrenal was the only other organ containing a tuberculous lesion. In another case the lesions in the adrenal were associated with tuberculosis of the liver and with a healed primary pulmonary lesion. Among the colored, 32 of the 55, or 58 per cent, showed miliary tubercles of varying size and number, a percentage which almost coincided with 57

in the white. Extensive, conglomerate lesions were noted among the colored in the remaining 23 cases. It is evident that there are no racial differences in the character or type of the lesion in the adrenal.

THYROID

The incidence of tuberculous involvement of the thyroid is the same in the two races. Tuberculosis of the thyroid was associated with generalized miliary involvement. The lesions in the gland were miliary in nature and few in number.

OSSEOUS SYSTEM

The bones were involved in 9 instances or 2.7 per cent among the white personnel. In 7 cases there was a tuberculous spondylitis, which in 2 cases was associated with a tuberculous pneumonic lesion, in the remaining 5 cases with generalized miliary tuberculosis. In 2 instances the dorsal vertebrae were involved, in 3 the thoracic, and in 2 the lumbar. Tuberculosis of the femur and ilium was associated in one case with miliary tuberculosis of the spleen and liver and pulmonary apical scar. Among the colored the vertebrae were involved in 19, or 7.5 per cent, of cases: the process was in the thoracic and lumbar region in 8 each, in the dorsal vertebrae in 2, and in the cervical vertebrae in 1. In 3 instances the tuberculous spondylitis was associated with pulmonary tuberculosis, in 2 there was associated meningitis with no active lesion in other organs, while in 14 there was an associated miliary tuberculosis. In 3 instances there was a tuberculous involvement of the second and third ribs.

EARS

The middle and internal ear were involved in 3 white and 2 colored. Among the white persons the petrous portion of the bone had eroded but there was no meningitis in 2 cases although it was present in the third. In the colored both lesions were associated with generalized miliary tuberculosis and 1 with meningitis.

EYE

The eyes were involved in 2 white persons. In one instance miliary tubercles were noted in the retina, while in the second case rare epithelioid tubercles were found in the choroid.

SUMMARY

1. During World War II the annual mortality from tuberculosis in the U. S. Army, per 100,000, was 6.7, while among the civilian population during 1940 the rate was 47.7. In World War I the incidence among military personnel was 65.9, and in the civilian population in 1920 it was 151.4 per 100,000.

2. Autopsy records of 329 white and 252 colored, who died from tuberculosis in Army hospitals during the period from December 1941 to December 1945, were analyzed.

3. Despite uniformity of living conditions, income and military duties, the colored, representing about 10 per cent of the Army population, contributed 43.4 per cent of the deaths from tuberculosis.

4. The distribution of fatal tuberculosis was in general comparable among the whites and colored for the same age groups, same periods of service, same places of service. The exception is the higher rate among white Army personnel in 1945 in foreign service, due in part to the return of tuberculous prisoners of war.

5. The short duration of the tuberculous process in both races, but especially in the white, is attributable to the frequency of tuberculous meningitis.

6. In general, no significant racial difference was noted in the occurrence of tuberculosis in many of the organs, but among the white the central nervous system, the seminal vesicles, and prostate were more commonly affected, and among the colored, the hilar

nodes, peritoneum, and vertebrae.

7. Evidence of healed primary tuberculosis in the lungs and in the tracheobronchial nodes was seen more often among whites. Among the colored, pulmonary lesions were more frequently ulcerative in character.

BIBLIOGRAPHY

¹ Dempsey, M.: Statistical data; new cases of tuberculosis discovered by case-finding surveys. *Am. Rev. Tuberc.* 48: 58-63, 1943.

² Wright, S., and Lewis, P. A.: Factors in the resistance of guinea pigs to tuberculosis, with especial regard to inbreeding and heredity. *The American Naturalist.* 55: 20-50, 1921.

³ Lewis, P. A., and Loomis, D.: Ulcerative types as determined by inheritance and as related to natural resistance against tuberculosis; experimental study on inbred guinea pigs. *J. Exper. Med.* 47: 449-468, 1928.

⁴ Küster, E., and Kröning, F.: Der Einfluss des Genotyps und der Einfluss äusserer Faktoren auf die Tuberkulose-resistenz beim Meerschweinchen. *Arb. a. d. Staatsinst. f. exper. Therap.* 35: 38-68, 1938.

⁵ Lurie, M.: Heredity, constitution and tuberculosis; experimental study. *Am. Rev. Tuberc. (suppl.)* 44: 1-125, 1941.

⁶ Aronson, J. D., Parr, E. I., and Saylor, R. M.: BCG vaccine; its preparation and local reaction to its injection. *Am. Rev. Tuberc.* 42: 651-666, 1940.

⁷ Israel, H. L., and Payne, H. M.: Tuberculosis in negro; clinical and roentgenological characteristics. *Am. Rev. Tuberc.* 41: 188-209, 1940.

⁸ Opie, E. L.: Active and latent tuberculosis in negro race. *Am. Rev. Tuberc.* 10: 265-274, 1924.

⁹ Everett, F. R.: Pathological anatomy of pulmonary tuberculosis in American negro and in white race. *Am. Rev. Tuberc.* 27: 411-464, 1933.

¹⁰ Pinner, M., and Kasper, J. A.: Pathological peculiarities of tuberculosis in American negro. *Am. Rev. Tuberc.* 26: 463-491, 1932.

¹¹ Tuberculosis in the United States. National Tuberculosis Association and U. S. Public Health Service, 1943.

¹² Rogers, J. B.: Comparison of gross tuberculous lesions in whites and negroes. *Am. Rev. Tuberc.* 4: 669-675, 1920.

¹³ Opie, E. L.: Anatomical characteristics of tuberculosis in Jamaica. *Am. Rev. Tuberc.* 22: 613-625, 1930.



FIBROUS DYSPLASIA OF SINGLE BONES (MONOSTOTIC FIBROUS DYSPLASIA)*

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(With thirty-four illustrations)

INTRODUCTION

SIXTY-SEVEN cases of fibrous dysplasia involving a single bone, which were studied at the Army Institute of Pathology, provide the basis for this paper. It considers first, the clinical manifestations, roentgenologic findings, pathologic anatomy, and location of the lesions; second, the relation of monostotic fibrous dysplasia to certain other conditions involving bones; and finally, the part played by trauma in its production.

The proliferation of connective tissue is one of the basic responses of the body to injury; usually it is an integral part of the process of repair. When it occurs in the medullary cavity of bone it is frequently given the distinctive name "osteitis fibrosa," although in the bones, as in other organs of the body, connective tissue overgrowth is a nonspecific reaction. It occurs, for example, in chronic osteomyelitis, in osteomalacia and rickets, following prolonged acidosis, and in the vicinity of primary and metastatic tumors of bone. Such connective tissue replacement of the marrow cavities and adjacent cancellous bone is also a characteristic feature of certain systemic diseases, namely von Recklinghausen's disease (generalized osteitis fibrosa cystica) and Paget's disease (osteitis deformans). In the former the fibrosis is secondary to an increase in the rate of bone resorption following enhanced activity of the osteoclasts, and decalcification of the bone trabeculae due to an associated hyperparathyroidism. In Paget's disease osteoclastic destruction of bone is less intense and new bone formation is accelerated. The irregular, partially calcified trabeculae do not form symmetrical Haversian systems but are united in a haphazard fashion by broad cement lines to provide the "mosaic pattern"

described by Schmorl.¹ These two diseases are further characterized by changes in blood chemistry. In von Recklinghausen's disease hyperfunction of the parathyroids leads to an increase in the serum calcium and phosphatase, a decrease of inorganic phosphorus, and excessive excretion of calcium and phosphorus in the urine. In Paget's disease serum calcium and phosphorus levels are essentially normal but there is an increase in the serum phosphatase.

During the past decade another disease, different from Paget's and von Recklinghausen's, but associated with fibrosis and deformity of bones, has been recognized. This was perhaps first reported by Weil² in 1922, but not until 1937 was it generally accepted as a distinct entity. In that year McCune and Bruch³ published a detailed account of what they called a case of osteodystrophia fibrosa combined with precocious puberty and pathologic pigmentation of the skin in a young girl. In the same year Albright, Butler, Hampton and Smith⁴ described a "syndrome characterized by osteitis fibrosa disseminata, areas of pigmentation and endocrine dysfunction, with precocious puberty in females." Their clinical findings are now frequently referred to as "Albright's syndrome." The following year Lichtenstein⁵ reported 8 cases, and suggested the term "fibrous dysplasia of bone" to identify the disease. In 1942 Lichtenstein and Jaffé⁶ described 15 additional cases with a comprehensive study of the gross and microscopic changes and a review of the literature. These authors were able to collect 75 previously reported cases which, with their own, brought the total to 90. The sex of the patient was known in 86 of these; 51 were female and 35 male. In only 32 of the 90 cases was any degree of cutaneous pigmentation noted. Only 20—all females—showed clinical evidence of endocrine dysfunction, characterized by precocious puberty, early skeletal maturation, and

* From the Army Institute of Pathology, Washington 25, D.C.

extensive bone lesions. Serum calcium, phosphorus, and phosphatase levels were within normal limits. In 15 of 87 cases only a single bone was affected; however, Jaffé and Lichtenstein pointed out that monostotic involvement is probably much more common than these figures would indicate. Their suggestion is supported by the cases which provide the material for this paper.

MATERIAL STUDIED

During the war material and records from 69 cases of fibrous dysplasia of bone were studied at the Army Institute of Pathology. The lesion was confined to a single bone in 67, involved both the right femur and tibia in one and was polyostotic in another. The almost complete absence of multiple bone involvement in this series may be due to recognition of the condition upon examination at induction centers with consequent disqualification for military service. In 2 cases, monostotic lesions visible in roentgenograms of the chest made at the time of induction went unrecognized, with the result that the inductees were accepted for general military service. Only 5 of the patients were females, but this is of no statistical significance in view of the selective nature of the group examined. Two of the men were Negroes, the others were white. The average age at the time of the onset of symptoms was 26 years. Again, this figure has little meaning since the study was restricted to members of the military age group, that is, between 18 and 38 years.

CLINICAL MANIFESTATIONS AND ROENTGENOLOGIC FINDINGS

The first sign of disease was usually a local swelling, particularly if the affected bone was superficial, e.g. the skull, ribs, and tibia. Local tenderness was sometimes associated with the swelling, and occasionally, when one of the long bones was involved, pain of an arthritic character was referred to the nearest joint. The lesion was not suspected in 4 cases until the patient suffered a pathologic fracture; in 3 it was in the femur, in 1 in the tibia. In 12 of the 29 cases in which a rib was involved

there were no symptoms; the abnormality was discovered in a roentgenogram of the chest taken for other reasons. Such an asymptomatic lesion was also found once in an ulna and again in a tibia. Extension of the process was usually slow. Thus 5 lesions were observed for approximately 18 months, and 1 for 4 years, during which time they showed no change. A lesion in the greater trochanter of a femur remained stationary for 13 months. On the other hand, one in a rib doubled in size within 2 years.

In contrast to many of the reported cases of polyostotic fibrous dysplasia none of the cases of the monostotic form showed areas of abnormal skin pigmentation or evidence of endocrine disturbances. No congenital anomalies were encountered. In 18 cases in which serum calcium, phosphorus, and phosphatase determinations were reported the values were within the normal range.

When the lesion was confined to one of the ribs, simple excision of the affected portion gave wholly satisfactory results. In the long bones curettement usually was performed and the defect then filled with bone chips; the implanted bone was slowly resorbed and replaced by healthy callus. It is interesting to note that fracture followed curettement in 4 cases; twice this occurred in the femur, once in the fibula, and once in the humerus. In 1 case the fracture occurred as late as 6 months after operation. The fractures all healed promptly.

The prognosis in monostotic fibrous dysplasia is uniformly good. The cases comprising the series here reported have been followed for less than 3 years after operation, but during this time none have shown signs of recurrence. There is no evidence in our material that the monostotic form of fibrous dysplasia may progress to the polyostotic variety.

Roentgenologic findings. The appearance of monostotic fibrous dysplasia in the roentgenogram offers little that is characteristic. In the long bones the lesions were found principally in the metaphyses (Fig. 1, 2 and 3), though occasionally they occupied the middle

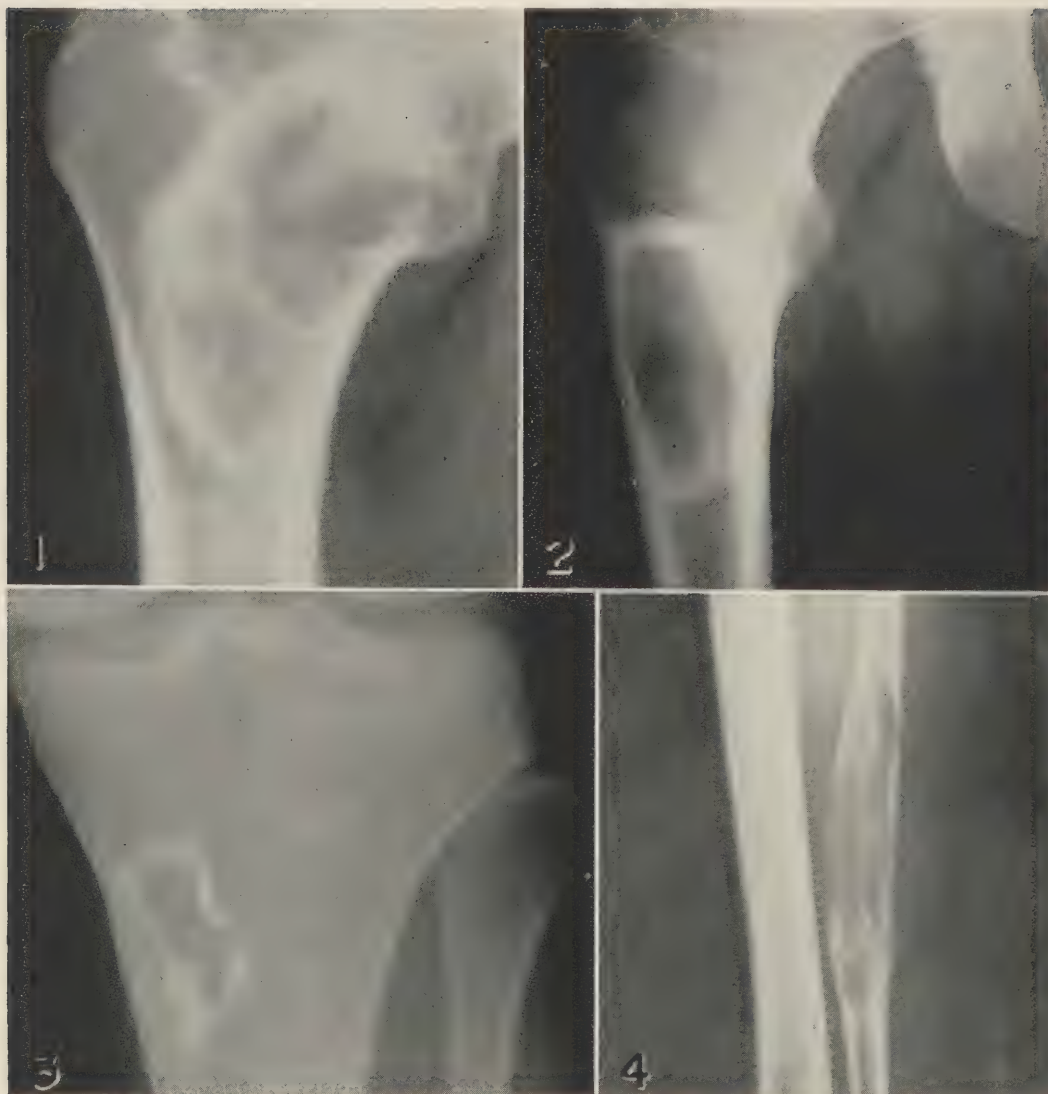


FIG. 1. Case 51. Fibrous dysplasia of the subtrochanteric region of the left femur.

FIG. 2. Case 54. Fibrous dysplasia of the proximal metaphysis of the left femur. Note the unusually broad area of bone condensation about the lesion.

FIG. 3. Case 63. Fibrous dysplasia of the proximal metaphysis of the right tibia. The eccentric position of the lesion is noteworthy, for this localization is frequently regarded as characteristic of so-called non-osteogenic fibroma of bone.

FIG. 4. Case 67. Fibrous dysplasia in the diaphysis of the right fibula.

of the shaft (Fig. 4). No site of predilection was noted in the ribs. When the skull was affected the maxilla was most often involved.

In the roentgenogram the area of fibrous dysplasia is radiolucent, sometimes traversed by delicate trabeculae of bone (Fig. 5 and 6). It is usually central in position and produces thinning and expansion of the cortex, particu-

larly marked in the ribs and fibula (Fig. 6 and 4) and in the bones of the calvarium; at times there is a narrow margin of condensed bone at the periphery (Fig. 7 and 2).

The nonspecificity of the roentgenogram in this disease is emphasized by the fact that in not one of our cases was the possibility of fibrous dysplasia entertained by the roentgen-

ologist. The differential diagnoses offered were in order of frequency: bone cyst 16, giant cell tumor 8, osteochondroma 8, tumor 7, enchondroma 4, chondroma, fibroma, ossifying fibroma, osteitis fibrosa cystica, sarcoma 2, and myeloma 2. Osteoma, chondromyxoma, non-osteogenic fibroma, adamantinoma, Ewing's tumor, eosinophilic granuloma of bone, Paget's

resected ribs. The lesions appeared as symmetrically fusiform or almost spherical swellings ranging up to 6 cm. in greatest diameter. The surface consisted of thin but intact cortical bone. On longitudinal section the cancellous bone and marrow of the rib were found to be replaced by a firm, resilient, yellow-white tissue containing occasional small cysts, usually

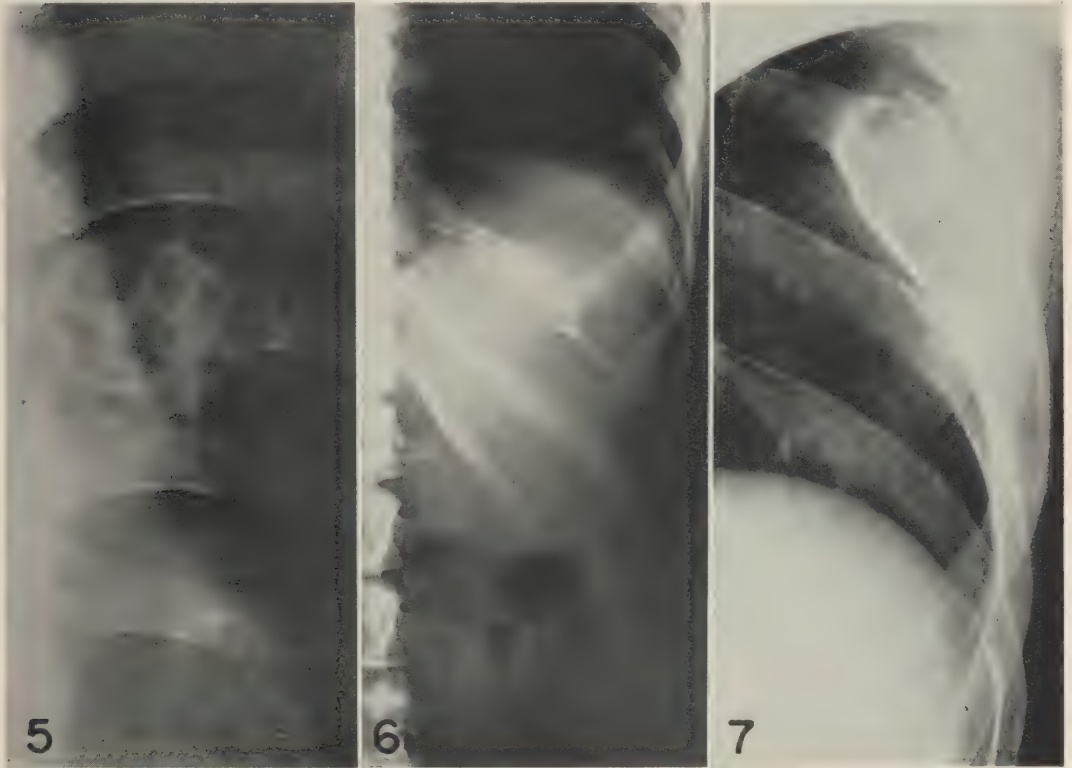


FIG. 5. Case 33. Fibrous dysplasia of the left 7th rib at its junction with the vertebra. Remnants of bone trabeculae give the lesion a multiloculated appearance.

FIG. 6. Case 44. Fibrous dysplasia of the right 10th rib.

FIG. 7. Case 35. Fibrous dysplasia of the left 7th rib. Note condensation of the cortical bone.

disease, osteomyelitis, and callus each appeared once. The fact that the diagnosis of fibrous dysplasia is not found among these 21 diverse opinions would indicate that many roentgenologists are still unaware of the importance of considering this disease in the differential diagnosis of a solitary bone lesion.

PATHOLOGIC ANATOMY

The gross appearance of the involved bones in the present series has been studied in 18

filled with amber fluid (Fig. 8). The transition from the pathologic to the normal bone marrow was often abrupt (Fig. 9). The abnormal tissue had a gritty character due to the presence of innumerable minute spicules of bone.

When skull or long bones were involved, only fragments obtained by curettement were available for examination; grossly these resembled the lesions in the ribs.

Histologically the primary component of the bone lesion is connective tissue, fairly well

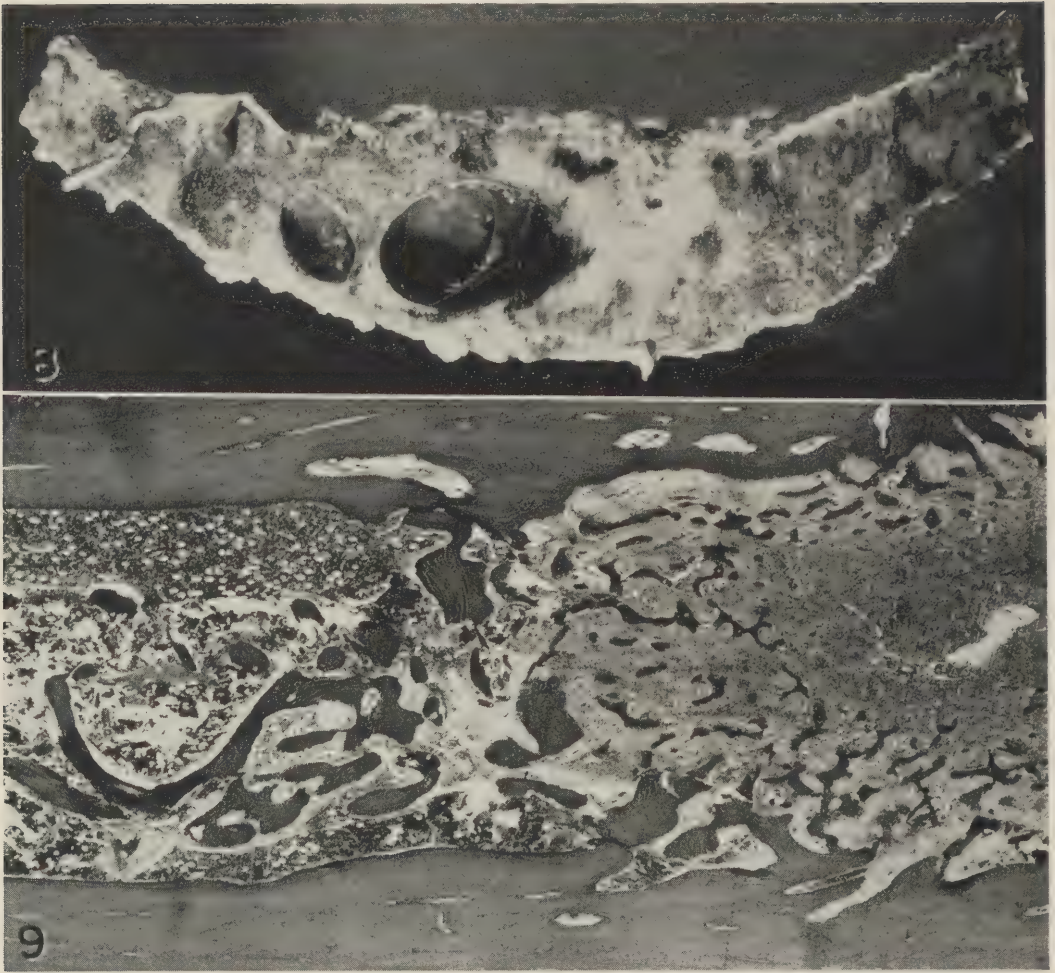


FIG. 8. Case 21. Longitudinal section through the posterior half of the 3rd rib. The cortex is thin, the bone expanded by firm, white, somewhat gritty fibrous tissue. The two cysts were filled with amber blood-tinged fluid; such relatively large cysts are uncommon.

FIG. 9. Case 43. Junction of normal marrow and an area of fibrous dysplasia in a rib. The pathologic tissue occupies the right half of the figure. Note that the pre-existing cancellous bone appears to inhibit spread of the connective tissue. Spicules of metaplastic bone occupy its periphery; they are not remnants of the original bone trabeculae. Hematoxylin and eosin stain. $\times 15$.

vascularized and frequently arranged in interlacing bundles and whorls (Fig. 10). Within the connective tissue, and most abundant at its periphery, are trabeculae of partly calcified newly formed bone (Fig. 9 and 11). That this bone is formed by direct metaplasia of the connective tissue is clearly evident from a study of the sections. The sequence of events appears to be as follows: the connective tissue cells round up, the nuclei become vesicular, and the intercellular fibrils thicken and stain deeply with eosin (Fig. 15). Subsequently the inter-

cellular substance increases in amount and ultimately becomes calcified. The incarcerated connective tissue cells are then indistinguishable from osteocytes (Fig. 16). Even the more mature trabeculae are deeply penetrated by bundles of collagenous fibers (Fig. 17). Not infrequently the trabeculae of new bone form an arch or complete circle about an area of edematous connective tissue (Fig. 12). This is usually found in lesions of the long bones, and is uncommon in those of the ribs. It may be linked to the probability that the lesions in the

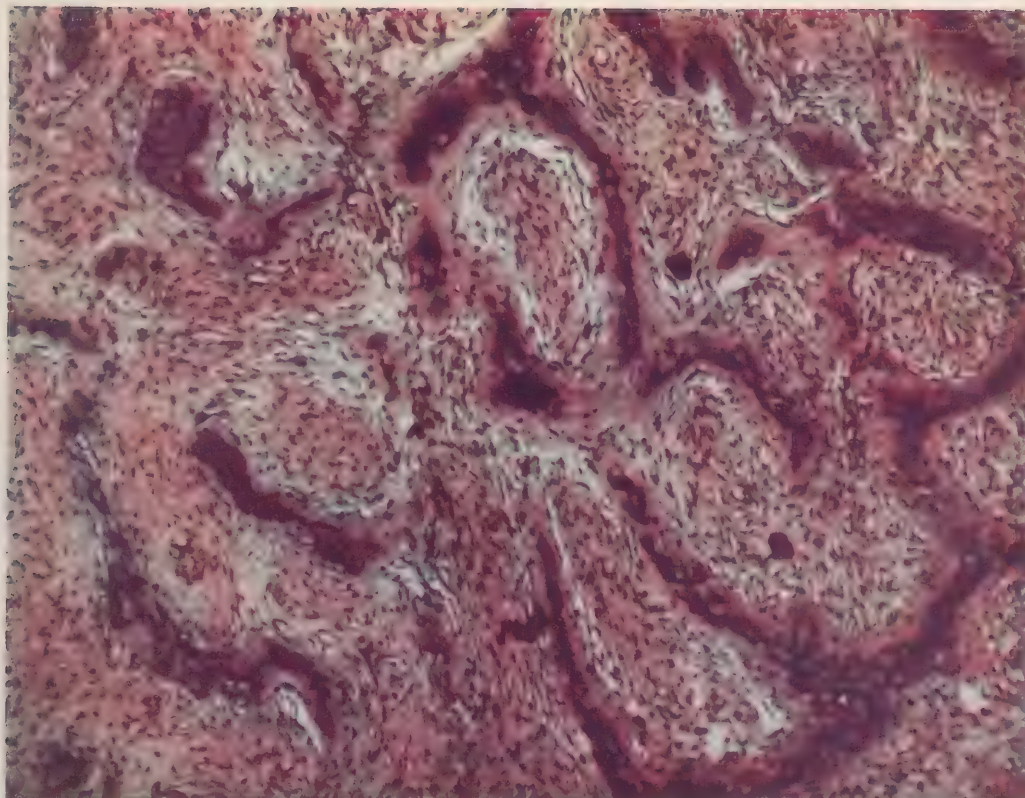


FIG.
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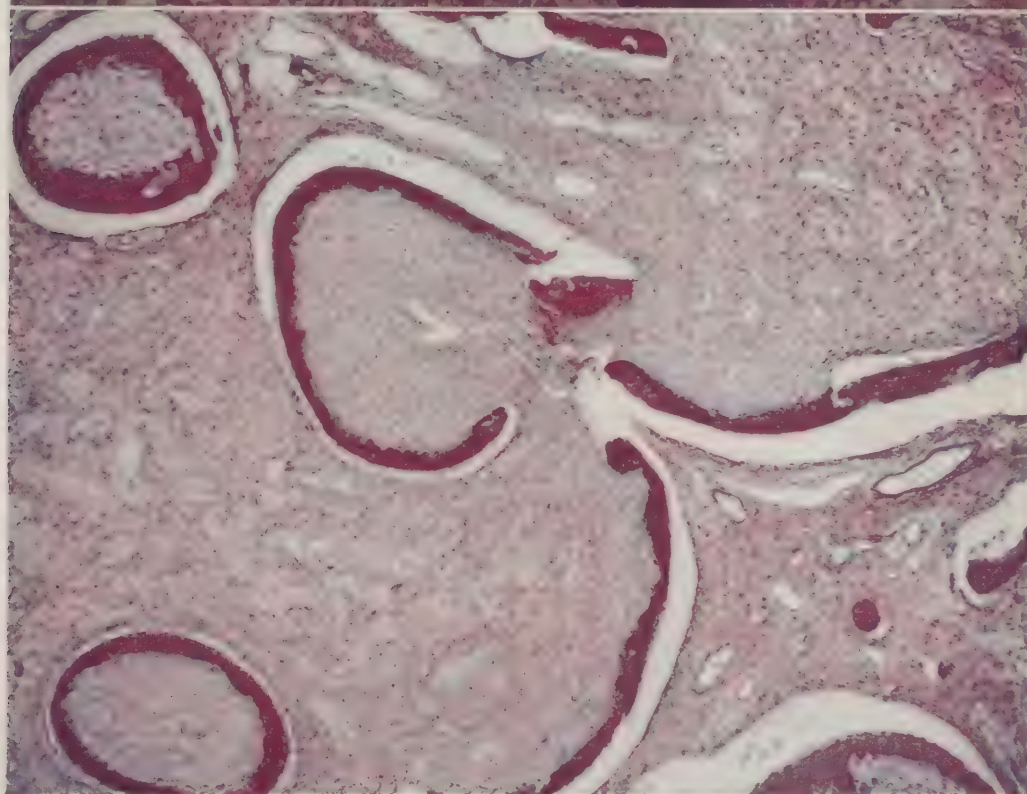


FIG.
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FIGURE 11. Case 43. Trabeculae of metaplastic bone are developing within fairly dense connective tissue. The periphery of the bone spicules is not calcified. This is the histologic appearance most characteristic of fibrous dysplasia. Hematoxylin and eosin stain. X150.

FIGURE 12. AIP Acc. 125831. Section from a biopsy of the right trochanter in a case of the monomelic type. The long curved spicules of bone appear to be developing at the junction of loose edematous connective tissue and a more dense fibrous tissue. The spaces are chiefly artefact, rarely they are vascular channels. The bone trabeculae are more mature than those in Fig. 11 and are sometimes found in lesions of the long bones but are uncommon in the ribs. Phosphotungstic acid hematoxylin stain. X60.

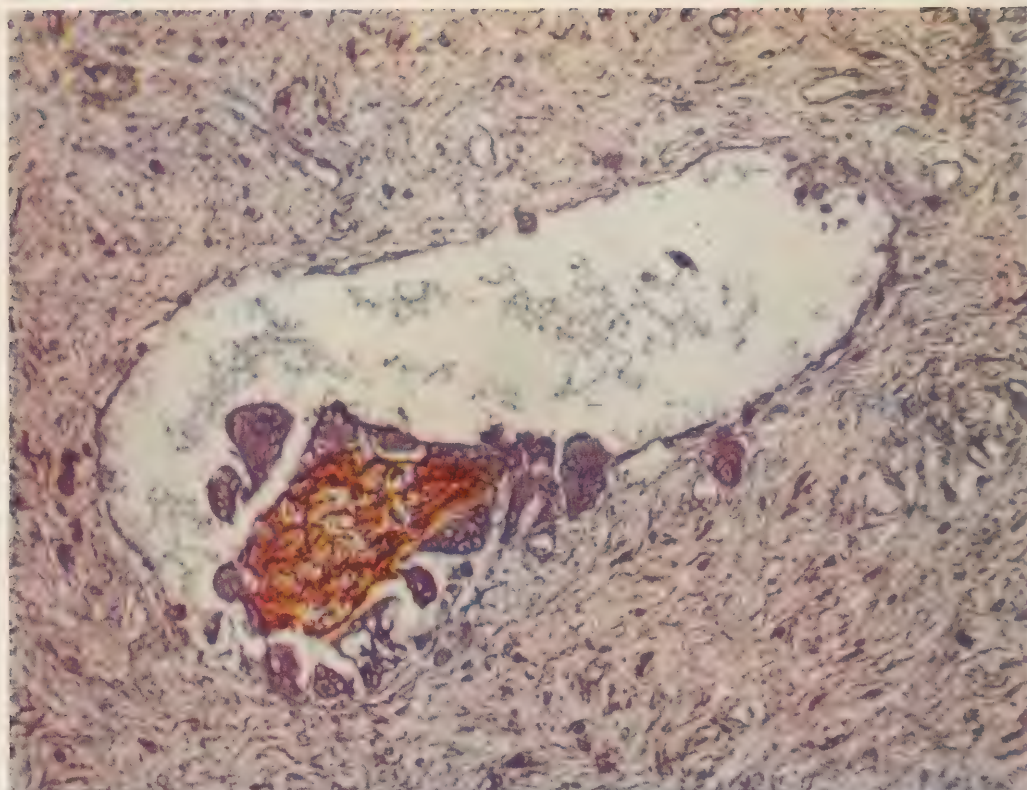


FIG.
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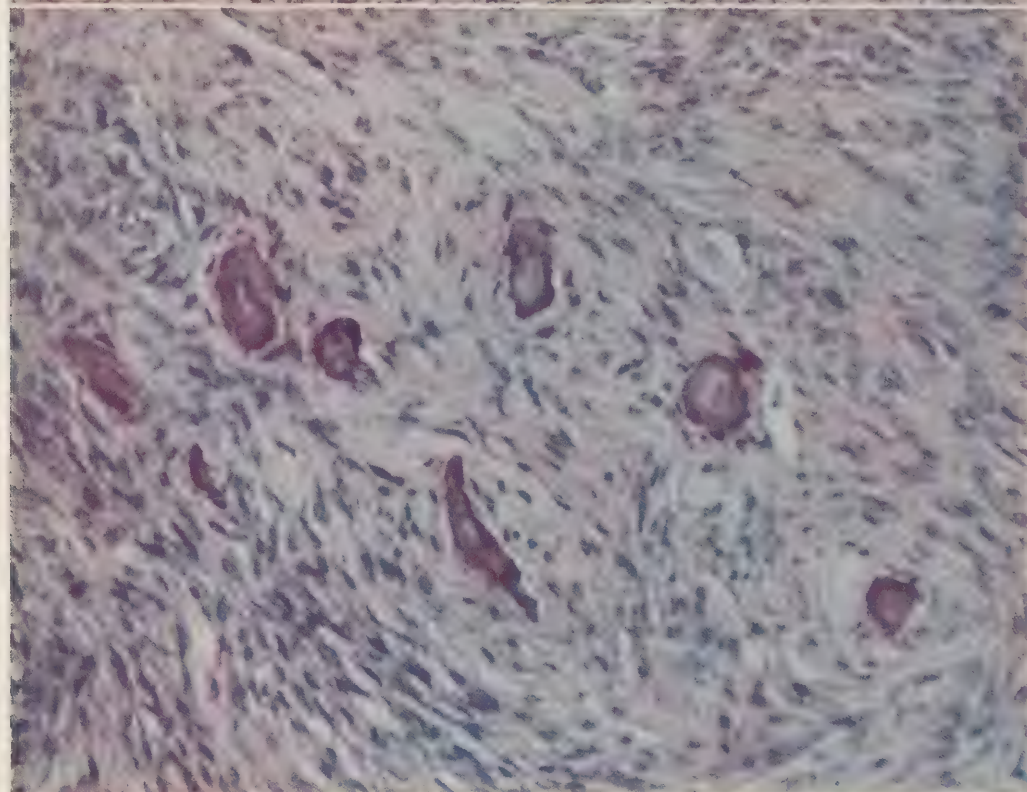


FIG.
14

FIGURE 13. Case 34. Cyst formation following osteoclastic destruction of bone and its replacement by tissue fluids rather than by proliferation of fibrous tissue. A remnant of metaplastic bone is being destroyed by osteoclasts within the cyst. Phosphotungstic acid hematoxylin stain. X₁₄₅.

FIGURE 14. Case 12. Histologic appearance of a so-called ossifying fibroma of the right maxilla; see also Figs. 32 and 33. This is merely a variant of the more typical lesion of fibrous dysplasia shown in Fig. 11. Hematoxylin and eosin stain. X₂₃₀.

bones of the extremities are somewhat older when discovered, and hence the trabeculae are larger. The production of this fibrous bone under normal and various pathologic conditions has been exhaustively studied by Weidenreich⁷ and Leriche and Policard.⁸

Occasionally the connective tissue cells, after rounding up, apply themselves to the periphery of the metaplastic bone as osteoblasts. Associated with these may be large multinucleate cells, osteoclasts, which appear to break down the newly formed bone (Fig. 18). Occa-

were not observed in our material except in conjunction with healing pathologic fractures (Fig. 20). Such fractures were found in 3 of the 18 ribs examined grossly; there was evidence of periosteal bone formation as well as endosteal callus (Fig. 21).

The diagnoses offered by the pathologists who submitted the bones to the Army Institute of Pathology were varied: the lesion was diagnosed as fibrous dysplasia in 19 cases, osteitis fibrosa in 13, giant cell tumor in 7, ossifying fibroma in 7, fibrosarcoma in 5,

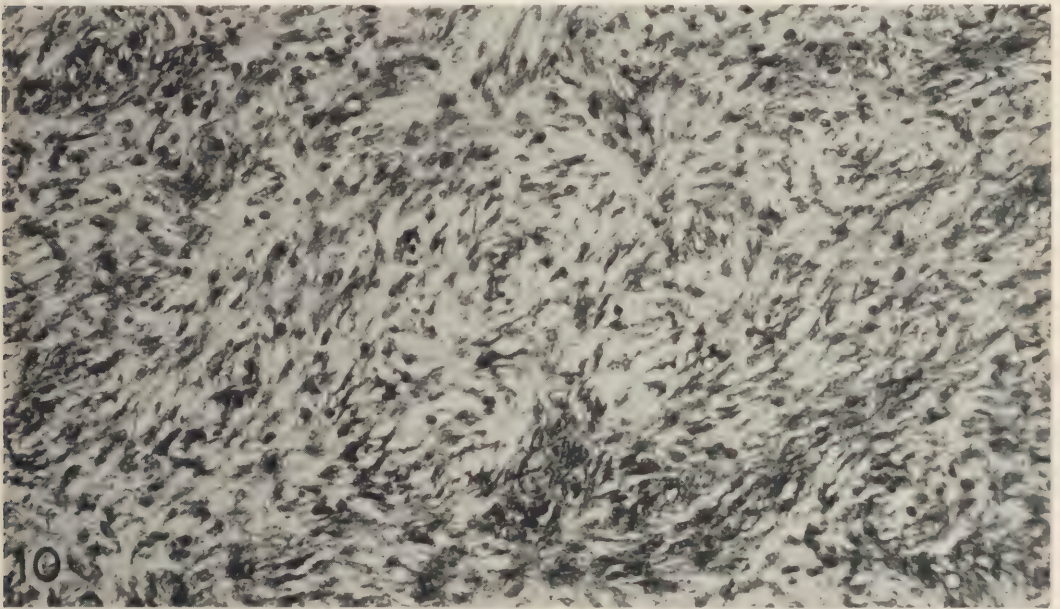


FIG. 10. Case 42. Characteristic whorled character of the connective tissue element in fibrous dysplasia. Hematoxylin and eosin stain. $\times 230$.

sionally this osteoclastic removal of bone leads to the formation of small cysts (Fig. 13).

While metaplastic bone formation is a prominent feature of fibrous dysplasia, there are sometimes large areas in which no such osseous transformation of connective tissue is evident (Fig. 19). No histologic differences are apparent between this connective tissue which exhibits no tendency to form bone, and that which does. It is noteworthy, however, that osseous metaplasia is more evident at the periphery of the lesions, that is to say, in regions adjacent to pre-existing bone.

Islets of cartilage, reported by some authors,

fibroma in 3, bone repair in 3, osteodystrophy in 2, bone cyst in 2 cases; hyperostosis, fibromyxoma, osteoid osteoma, and chronic inflammation were each reported once. From the number of correct diagnoses it would appear that pathologists are becoming increasingly aware of fibrous dysplasia as a distinct entity, although a considerable number are still classifying it under the nondescript term "osteitis fibrosa." However, the fact that the diagnosis of fibrosarcoma was sometimes made indicates that there is still work to be done in familiarizing pathologists with this lesion and in stressing its benign character.

TABLE I
BONES INVOLVED: SKULL, VERTEBRA, PELVIS

Case No.	Age**	Site of Lesion	History of Trauma	Duration of Symptoms	Local Swelling	Local Tenderness	Blood Ca, P, Phosphatase	Curettement—C	X Ray Diag.	Path. Diag.	Remarks
1. 97645	21	Left frontal bone	—	7 mos.	+	—		C	Fibroma	Osteofibroma, hyperostosis	Left eye was displaced downward; intermittent headaches.
2. 168845	23	Right frontal bone	—	6 yrs.	+	—		C		Fibromyxoma	
3. 120904	21	Left parietal bone	—	7 yrs.	+	—	Normal	C	Tumor	Osteitis fibrosa	
4. 130727	25	Left mastoid	—	12 yrs.	+	—	Normal	C	Paget's disease, osteoma	Fibrous dysplasia	Frequent earache and discharge from left ear until 12 years old.
5. 122552	25	Occipital bone, center	—	1 yr.	+	+		E	Osteochondroma	Fibrous dysplasia	Pain and limitation of motion in back of neck.
6. 94650	23	Left maxilla	—	4 mos.	+	—		C		Ossifying fibroma	
7. 116477	27	Left maxilla	—	4 mos.	+	—		C		Periosteal fibrosarcoma	
8. 164352	22	Left maxilla	—	10 yrs.	+	—		C		Reactive bone proliferation	
9. 94803	15	Right maxilla	—	9 mos.	+	—		C		Osteofibroma	Onset of symptoms followed a toothache.
10. 102554	26	Right maxilla	—	2 mos.	+	—		C	Ossifying fibroma	Ossifying fibroma	Recent onset of diplopia.
11. 110804	24	Right maxilla	—	6 mos.	+	—		C	Fibro-osteoma	Fibro-osteoma	Growth recurred after initial removal.
12. 135364	34	Right maxilla	—	3½ yrs.	+	—		C	Neoplasm	Ossifying fibroma	
13. 108696	22C	Right mandible	—	12 yrs.	+	—		C	Cyst	Fibrous dysplasia	
14. 126502	37	Right mandible	—	6 mos.	+	—		C	Adamantinoma	Ossifying fibroma	
15. 99474	20	4th cervical vertebra	+	11 mos.	—	+		C	Giant cell tumor, sarcoma	Giant cell tumor	Fractured 5th cervical vertebra 7 months before onset of symptoms.
16. 85995	47	Right ilium	—	?	—	—	Normal	C		Osteodystrophia	"Rheumatic" pains for many years.

* Army Institute of Pathology.

** The race is white, the sex male. If otherwise, it is so indicated.

DISTRIBUTION OF BONE LESIONS

The overall distribution of the 67 isolated bone lesions has been graphically represented in Figure 22. The number of times that the various bones were involved is as follows: ribs 29, femur 9, tibia 8, maxilla 7, calvarium 5, mandible 2, humerus 2, ulna 2, vertebra 1, pelvis 1, fibula 1. It is interesting to note that

Axial Skeleton: Skull, Vertebrae, and Pelvis: In the axial skeleton the bones of the skull were most often the site of monostotic fibrous dysplasia, with the maxilla the preferred location (Table 1). In 2 cases the lesion was present in the *frontal bone*; in 1 of these there was a history of intermittent headaches for 7 months. Physical examination revealed that

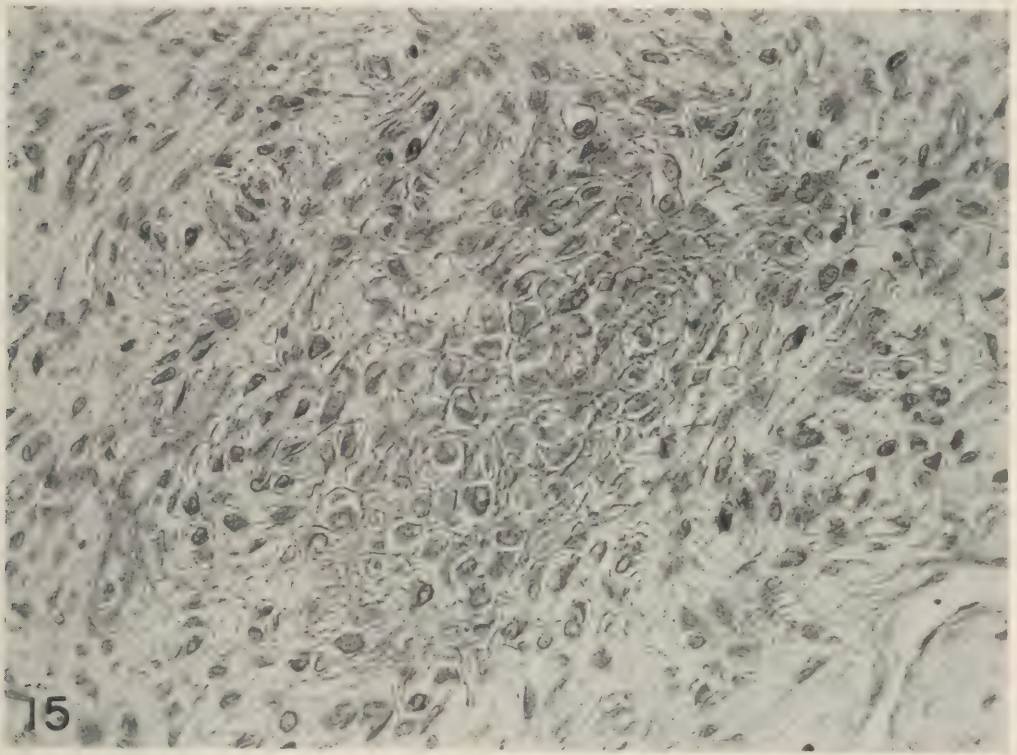


FIG. 15. Case 34. A very early stage in metaplastic fibrous bone formation. The connective tissue cells have rounded up; the fibrils in the intercellular matrix are more numerous and have an altered index of refraction. Phosphotungstic acid hematoxylin stain. $\times 300$.

in our series the small bones of the hands and feet were not affected. From Figure 22 it will be seen that although the distribution of the lesions is similar to that of many bone tumors and tumor-like conditions, involvement of the ribs is much more frequent than in other bone diseases. The cases in this series are presented according to their anatomic location, taking up, in order, those involving the axial skeleton, the ribs, the upper and lower extremities. For each group representative case histories are given.

the left eye had been displaced downward by thickening of the supra-orbital ridge and horizontal plate of the left frontal bone (Fig. 23). There was no loss of visual acuity. The patient stated that the bony malformations and associated malposition of the left eye had been present as long as he could remember.

The *parietal bone* (Case 3, Fig. 25) and *occipital bone* (Case 5, Fig. 24) were each once the site of fibrous dysplasia in the present series. The roentgenograms in these cases show quite clearly that the outer table was more

extensively thinned and expanded than the inner. This is true in the majority of cases with involvement of the calvarium, whether of the polyostotic or monostotic variety, reported in the literature.

It may be noted that most examples of the deforming disease of the skull known as

tion the content of the mastoid process was found to be extremely vascular and gritty, with the consistency of hard, dried-out cheese.

The *maxillary bone* was affected 7 times in the present series. A representative history is presented by Case 11. The patient was a 24-year-old white male who first became aware of

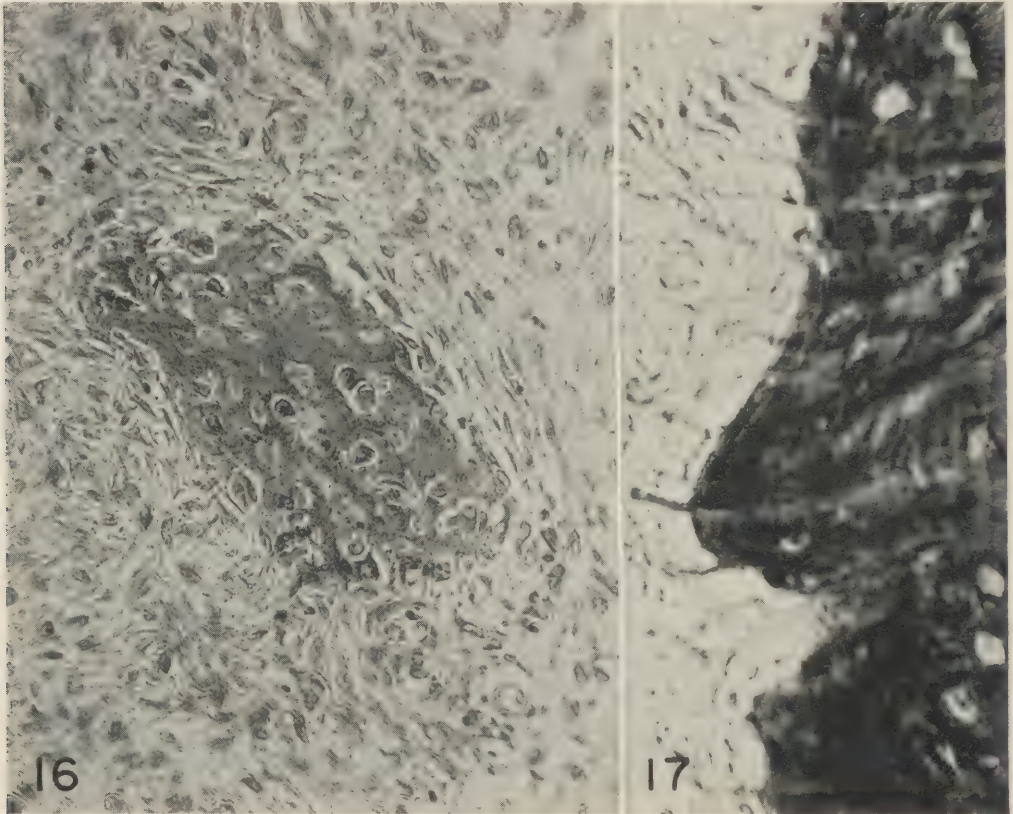


FIG. 16. Case 34. A more advanced stage in the development of metaplastic bone. The intercellular matrix is abundant and the incarcerated connective tissue cells have the appearance of osteocytes. Calcification has not yet occurred, the tissue may be identified as osteoid. Phosphotungstic acid hematoxylin stain. $\times 300$.

FIG. 17. Case 38. Stout connective tissue bundles pass from the fibrous tissue into a more mature trabecula of metaplastic bone, revealing the fibrous origin of the bone. Phosphotungstic acid hematoxylin stain. $\times 350$.

leontiasis ossea are regarded by Pugh⁹ and Falconer¹⁰ as fibrous dysplasia.

There was a single example of involvement of the mastoid process of the *temporal bone* (Case 4). The patient had suffered frequent earaches and aural discharge until he was twelve years old. Shortly thereafter his mother noticed a swelling behind the left ear, which slowly increased in size and was associated with intermittent pain in the area. At opera-

tion the content of the mastoid process was found to be extremely vascular and gritty, with the consistency of hard, dried-out cheese. The *maxillary bone* was affected 7 times in the present series. A representative history is presented by Case 11. The patient was a 24-year-old white male who first became aware of

slight asymmetry of his face 6 months before reporting for medical examination. About three and a half months later his dentist discovered an enlargement of the maxilla above the right bicuspid. Subjectively this soldier noticed disturbed tactile sensation over the right infra-orbital region and impaired vision in the right eye, lately associated with diplopia.

The *mandible* was involved in 2 cases. In 1, that of a 22-year-old colored soldier (Case

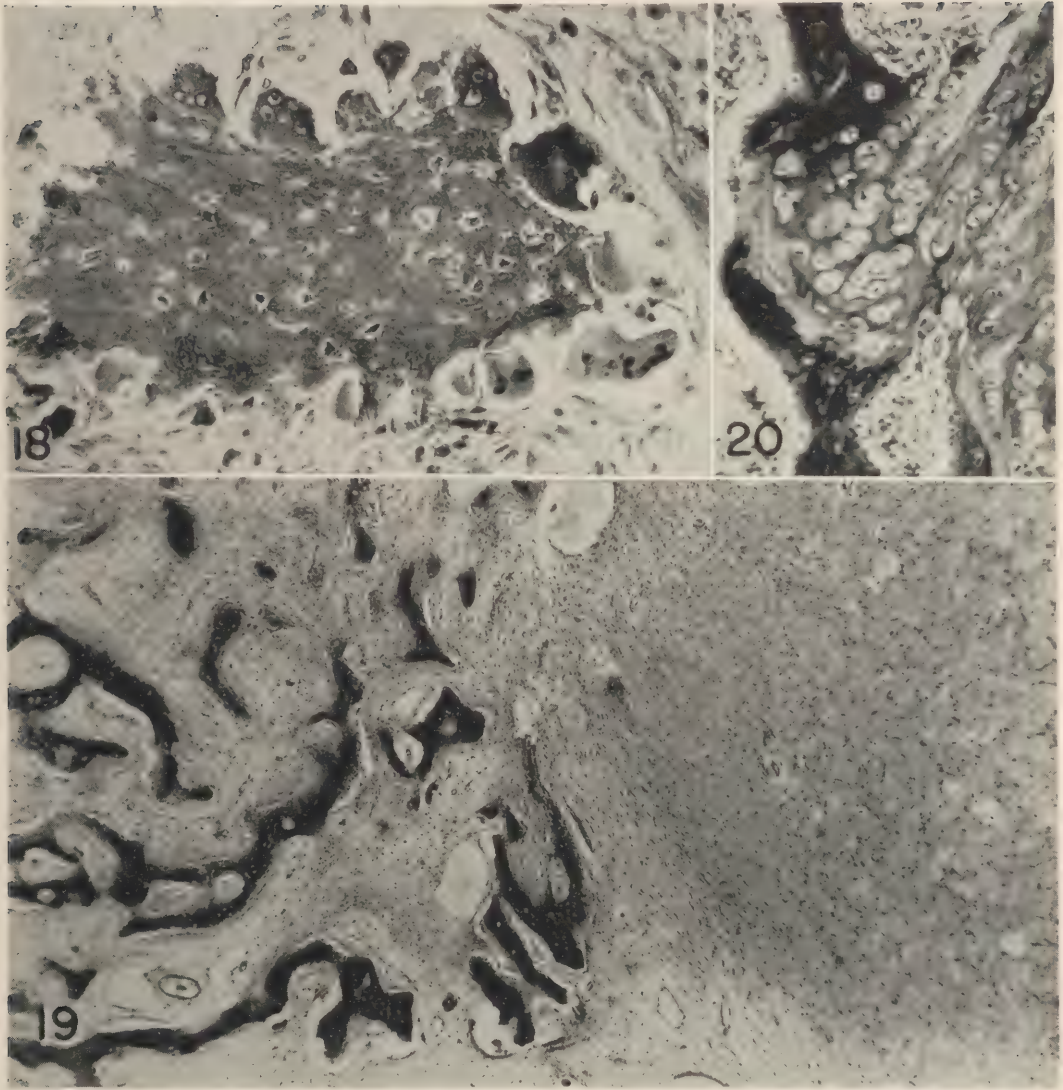


FIG. 18. Case 34. A spicule of metaplastic bone being destroyed by osteoclasts. This breakdown of newly formed bone accompanied the osteogenesis shown in figures 15 and 16. Phosphotungstic acid hematoxylin stain. $\times 300$.

FIG. 19. Case 56. The rather abrupt transition from actively osteogenic connective tissue to one which is nonosteogenic is well shown. The physicochemical factors responsible for this difference have not been determined. Hematoxylin and eosin stain. $\times 60$.

FIG. 20. Case 36. Cartilage at the site of a healing pathologic fracture through an area of fibrous dysplasia. Hematoxylin and eosin stain. $\times 115$.

13), the lesion grew slowly over a period of 12 years. An unsuccessful attempt was made to remove the growth, which at that time was diagnosed bone cyst. It remained painless, but reached such proportions (Fig. 26) that another operation was undertaken. In the second, the case of a 37-year-old white male (Case 14), the lesion was manifest for only

about 6 months during which it grew rapidly. A clinical diagnosis of adamantinoma was made.

The *vertebral column* was involved only once in our series (Case 15); the bone affected was the 4th cervical vertebra. Symptoms of local tenderness and pain radiating down both arms began 7 months after the

TABLE II
BONES INVOLVED: RIBS

Case No.	AIP* Acc. No.	Site of Lesion	Age**	History of Trauma	Duration of Symptoms	Local Swelling	Local Tenderness	Blood Ca, P, Phosphatase	Excision—E Currentment—C	X-Ray Diag.	Path. Diag.	Remarks
17.	122550	1st, right, posterior $\frac{3}{4}$	27	—	3 yrs.	+	—	—	E	Giant cell tumor, enchondroma	Fibrous dysplasia	Six years ago sudden pain over upper chest, felt something snap.
18.	123791	2nd, right, anterior	29	+	16 mos.	+	+	Normal	E	Osteochondroma	Bone cyst	Possible fracture while wrestling 12 years before.
19.	132100	2nd, right, axillary line	30C	—	—	—	—	—	E	—	Intramedullary fibroma	Incidental finding on chest film
20.	161586	2nd, anterior $\frac{3}{4}$	21	—	—	—	—	—	E	Bone tumor	Malignant giant cell tumor	Incidental finding on chest film.
21.	157355	3rd, posterior half	31	—	—	—	—	Normal	E	Giant cell tumor	Deferred	Incidental finding on chest film.
22.	97204	4th, left, anterior	25	+	1 yrs.	+	+	—	E	Myeloma, giant cell tumor	Fibrous dysplasia	Struck in region of clavicle 6 years ago, tender for 3 weeks.
23.	108976	4th, left, anterior	20	—	3½ yrs.	+	+	—	E	1940 old fracture 1944 chondroma myxoma	Fibrous dysplasia	—
24.	106133	4th, right, posterior $\frac{1}{4}$	24	—	8 mos.	—	+	Normal	E	Chondroma, giant cell tumor	Fibrous dysplasia	—
25.	93572	4th	23	—	2 yrs.	—	+	—	E	Sarcoma?	Osteitis fibrosa	—
26.	119366	5th, left, posterior	22	+	—	—	—	Normal	C	Metastatic malignancy	Fibrosarcoma	Six years ago fractured several ribs on left. Compression fracture of 4th and 5th D vertebrae.
27.	157045	5th, left, axillary line	37	+	2½ yrs.	—	+	Normal	E	Bone tumor	Fibrous dysplasia	Two-and-one-half years previously injury to left chest, 2 months later onset of pain.

28.	107992	6th, left, axillary line	34	—	8 yrs.	—	+	E	Bone tumor	Fibrous dysplasia Fibroma	Incidental finding on chest film.
29.	114907	6th, left, posterior	22	—	—	—	—	E	Osteochondroma	Fibrous dysplasia	Incidental finding on chest film.
30.	116461	6th, left, posterior	25	—	—	—	—	E	Enchondroma, giant cell tumor	Giant cell tumor	Incidental finding on chest film.
31.	94924	6th, right, posterior	28	—	—	—	—	E	Bone tumor	Osteitis fibrosa	Incidental finding on chest film.
32.	113477	6th, right, axillary line	19	—	—	—	—	E	Osteochondroma, myeloma, giant cell tumor	Osteodystrophia fibrosa	Pathological fracture.
33.	78123	7th, left, posterior	26	—	7 mos.	+	+	E	—	—	—
34.	111311	7th, left	23	—	2 mos.	—	+	E	—	Intramедullary fibrosarcoma	—
35.	113482	7th, left, axillary line	37	—	—	—	—	E	Osteochondroma	Osteitis fibrosa	Incidental finding on chest film.
36.	117404	7th, left, axillary line	22	+	1 yr.	—	+	E	Giant cell tumor	Fibrous dysplasia	Has been boxing for 4 years.
37.	134904	8th, right, posterior	26	—	1 yr.	+	—	Deep x-ray	—	—	—
38.	92648	9th, right, axillary line	36	—	—	—	—	E	Neoplasm	Fibro-osteochon- drosarcoma	Incidental finding on x-ray film.
39.	106268	9th, right, posterior	33	+	4 mos.	—	+	E	Bone cyst	Medullary fibrosis	Struck right chest 1 year ago.
40.	130731	9th, right, posterior	30	—	2½ yrs.	+	+	E	—	Osteoid osteoma	—
41.	156374	9th, right, posterior	37 ♀	—	—	—	—	E	Enchondroma	Fibrous dysplasia	Incidental finding on x-ray film.
42.	106908	10th, right, anterior	29C	+	8 yrs.	—	+	E	Osteochondroma	Fibrosarcoma	Crushed ribs on right side 8 years ago.
43.	107100	10th, right, anterior, medial	30	+	6 yrs.	+	+	E	Osteochondroma	Fibrous dysplasia	Fractured rib 3 times: 1931, '35, '36.
44.	146302	10th, right, middle	27	—	8 mos.	+	+	C	Osteitis cystica	Deferred	—
45.	154409	11th, right, posterior	34	—	—	—	—	E	—	Osteitis fibrosa	Incidental finding on x-ray film.

*Army Institute of Pathology.

** The race is white, the sex male. If otherwise, it is so indicated.

patient fractured his 5th cervical vertebra while driving a truck over an obstacle course; 4 months later another soldier struck him a blow on the neck. Biopsy of the vertebra showed the typical histologic pattern of fibrous dysplasia.

A lesion in the *right ilium* (Case 16) is the single instance of involvement of the pelvis (Fig. 27). It occurred in the only patient in this series who was above the 38-year limit for the military age group (47 years). He gave a history of repeated attacks of "rheumatism"

characteristic pattern of connective tissue and fibrous bone trabeculae (Fig. 4). Evidence of fracture was present in several cases; however, the fractures probably were incurred after the fibrous dysplasia was well advanced. At the site of fracture it was quite impossible to distinguish normal callus from the pathologic fibrous dysplasia (Fig. 21).

The relation of trauma to fibrous dysplasia of bone is suggested by certain cases in this series: Case 17. A 27-year-old white male

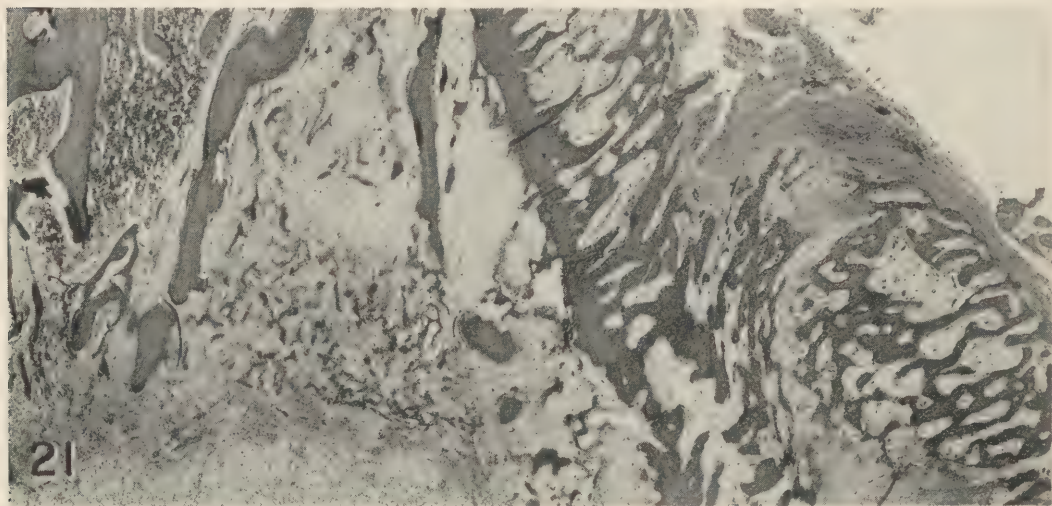


FIG. 21, Case 29. Periosteal new bone formation at the site of a pathologic fracture near the junction of normal and abnormal bone. Hematoxylin and eosin stain. $\times 15$.

for 25 years preceding discovery of the pelvic lesion. The role played by the latter in producing these symptoms, which involved his feet, knees, and hips, is questionable.

Ribs: The ribs were involved in 43 per cent of the cases in this series (Table 2). The fact that in 12 of the 29 cases the lesions of the rib were chance findings in roentgenograms of the chest taken for other purposes offers a partial explanation for this preponderance. The rib lesions usually showed symmetrical expansion and thinning of the cortex (Fig. 6 and 28); less often the cortical bone was condensed (Fig. 7). Occasionally the affected area assumed an almost spherical shape and was traversed by more or less stout trabeculae of bone (Fig. 26).

Histologically the rib lesions presented the

experienced sudden pain in the right shoulder and felt something snap while exercising. Within 3 weeks he was free of the resulting symptoms. Roentgenologic examination of the chest at an induction center 3 years later revealed a tumor-like deformity of the 1st rib. The patient was rejected at that time, but when he was inducted a year later the condition in the rib was unchanged.

Case 22. A 25-year-old white male was struck in the left upper chest while playing football in 1936. The area remained tender for about 3 weeks, after which symptoms subsided without specific treatment. He was inducted into the Army in June, 1942 and a routine roentgenogram of the chest disclosed a deformity of the left 4th rib which was interpreted as a congenital anomaly. A year

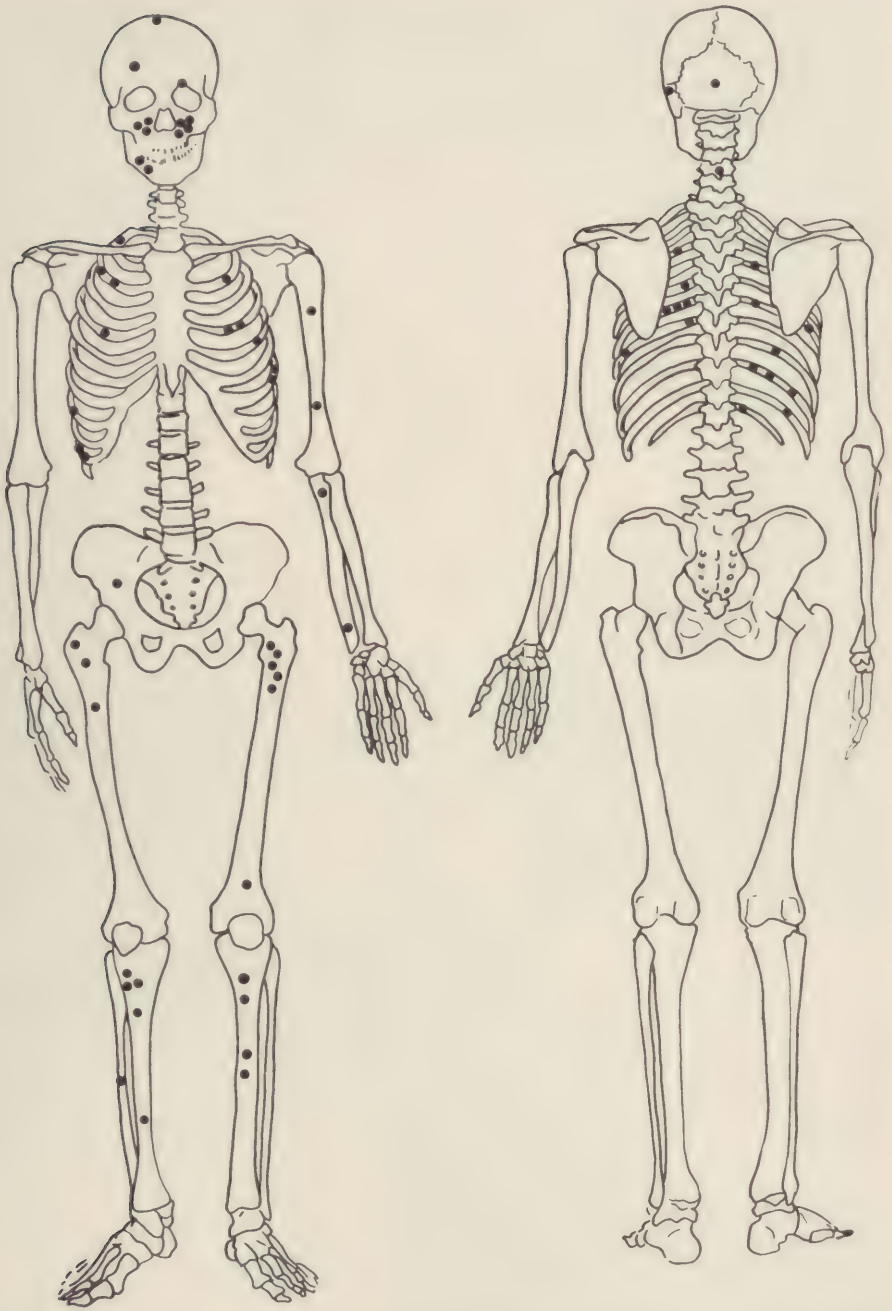


FIG. 22. Regional distribution of the lesions of monostotic fibrous dysplasia. Each dot on the skeleton represents a single instance.



FIG. 23. Case 1. Roentgenogram of the skull showing diffuse thickening of the left half of the frontal bone, with disappearance of the normal orbital outline.

FIG. 24. Case 5. Involvement of the occipital bone, with expansion of the diploe and thinning of the outer table.

FIG. 25. Case 3. Focal area of fibrous dysplasia in the left parietal bone.

TABLE III
BONES INVOLVED: HUMERUS AND ULNA

Case No.	AlP* Acc. No.	Site of Lesion	Age**	History of Trauma	Duration of Symptoms	Local Swelling	Local Tenderness	Blood Ca, P, Phosphatase	Curettement—C Excision—E	X-Ray Diag.	Path. Diag.	Remarks
46.	105267	Humerus, left, proximal	22		5 mos.	—	+	Normal	E	Focal infection	Brodie's abscess	
47.	161218	Humerus, left, distal	37 ♀		6 mos.	—	+	Normal	C	Bone cyst	Fibrous dysplasia	Pathologic fracture while under treatment.
48.	97435	Ulna, left, proximal	25			—	—		C	Bone cyst	Fibroma	Incidental finding in x-ray of elbow.
49.	105039	Ulna, left, distal	22	+	2 mos.	+	+		C	Ewing's tumor	Giant cell tumor	Injured arm in fall just prior to onset of symptoms.

* Army Institute of Pathology

** The race is white, the sex male. If otherwise, it is so indicated.

later, while attempting to leap over a tennis net the soldier fell, striking his left chest. Roentgenologic examination at that time led to a tentative diagnosis of myeloma or giant cell tumor. Histologic study of the excised tissue revealed that the lesion was fibrous dysplasia.

Case 27. A 37-year-old white soldier sustained an injury to the left anterior chest wall when he was thrown from his truck in March, 1943 during a blackout in Persia. He was free of symptoms until 2 months after the accident, when he suffered occasional pain, aggravated by deep breathing, over the left anterior aspect of his chest. In May, 1945, the pain became more severe and the soldier was hospitalized. At that time roentgenograms revealed "an extensive bone tumor involving almost the entire left 5th rib."

Upper Extremity: Humerus and Ulna: The upper extremity was involved 4 times; the humerus and the ulna each twice (Table 3). Duration of symptoms, which consisted primarily of local tenderness, ranged from 2 to 6 months. In Case 48 the lesion was found in the ulna following roentgenologic examination to discover the cause of pain in the elbow. A similar arthritic onset was present in Case 47. Early in 1945 a 39-year-old corporal in the WAC complained of arthritic pain in the left arm and was hospitalized with a provisional diagnosis of psychoneurosis. Roentgenologic examination revealed a "bone cyst" in the distal portion of the left humerus (Fig. 29). In April 1945 the lesion was curetted and the defect bridged by a bone graft. In November of that year the patient suffered a pathologic fracture (Fig. 30) and another bone graft was inserted. On February 19, 1946 roentgenologic examination revealed that the bone graft was well encapsulated and almost absorbed; there was satisfactory bony union. No fibrous dysplasia was demonstrated at this time.

Lower Extremity: Femur, Tibia, and Fibula: In the 9 cases in which the femur was involved, the lesion was found in the proximal end 7 times and in the distal end once; in the remaining case the location was

TABLE IV
BONES INVOLVED: FEMUR, TIBIA, FIBULA

Case No.	AIP* Acc. No.	Site of Lesion	Age**	History of Trauma	Duration of Symptoms	Local Swelling	Local Tenderness	Blood Ca, P, Phosphatase	Curettement—C	Excision—E	X-Ray Diag.	Path. Diag.	Remarks
50.	99152	Femur, left, distal	19		1 mo.	—	+		C	Eosinophilic granuloma	Osteitis fibrosa localisata	Osteitis fibrosa	Arthritic pain in left knee.
51.	101108	Femur, left, subtrochanteric	21			—	—		C	Bone cyst	Fibrous dysplasia	Fibrous dysplasia	Onset with pathologic fracture.
52.	104959	Femur, left, neck	22		3 mos.	—	+	Normal	C	Osteitis cystica	Osteitis fibrosa cystica	Osteitis fibrosa cystica	Pathologic fracture 6 months after curettement.
53.	128826	Femur, left, proximal	25			—	—		C	Bone cyst	Fibrous dysplasia	Fibrous dysplasia	Incidental finding on x-ray film.
54.	129463	Femur, left, proximal	19		1 yr.	—	+		C	Bone cyst	Osteitis fibrosa	Osteitis fibrosa	Onset with pathologic fracture.
55.	158202	Femur, left	27 ♀			—	—		C	Bone cyst	Giant cell tumor	Giant cell tumor	Onset with pathologic fracture.
56.	98059	Femur, right, proximal	18			—	—		C	Bone cyst	Repair of bone cyst	Repair of bone cyst	Onset with pathologic fracture, refractured 4 months later.
57.	130472	Femur, right, greater trochanter	37	+	2 yrs.	—	+	Normal	C	Bone cyst	Fibrous dysplasia	Fibrous dysplasia	23 years ago dislocated head and fractured neck of right femur.
58.	131033	Femur, right, trochanter	20 ♀		1 yr.	—	+		C	Cystic tumor	Osteitis fibrosa	Osteitis fibrosa	Symptoms began in 1st trimester of pregnancy.
59.	105123	Tibia, left, middle	21		4 yrs.	+	—		E	Bone cyst	Giant cell tumor	Giant cell tumor	
60.	127820	Tibia, left, proximal	33		6 mos.	—	+	Normal	C	Bone cyst	Bone cyst	Bone cyst	
61.	157068	Tibia, left, middle	24		Many yrs.	+	+	Normal	C	Osteochondroma	Fibrous dysplasia	Fibrous dysplasia	
62.	95795	Tibia, right, middle	21		3 mos.	+	+		C	Bone cyst	Osteitis fibrosa	Osteitis fibrosa	Bone cyst removed from right femur 7 years previously.
63.	100637	Tibia, right, proximal	30			—	—		C	Bone cyst	Osteitis fibrosa	Osteitis fibrosa	Incidental finding in x-ray after knee injury.
64.	101320	Tibia, right, proximal	23	+	3½ yrs.	+	+		C	Chondroma, nonosteogenic fibroma	Osteitis fibrosa	Osteitis fibrosa	Onset of symptoms after striking right knee.
65.	105196	Tibia, right, middle	20			—	—		C		Osteitis fibrosa	Osteitis fibrosa	Onset with pathologic fracture.
66.	128805	Tibia, right, middle	20		3 mos.	—	+		C	Bone cyst	Fibrous dysplasia	Fibrous dysplasia	
67.	139888	Fibula, right, middle	24		10 mos.	—	+	Normal	C	Enchondroma, fibroma	Osteitis fibrosa	Osteitis fibrosa	Pathologic fracture while under observation.

* Army Institute of Pathology

** The race is white, the sex male. If otherwise, it is so indicated.

not given (Table 4). None of the cases showed local swelling of the soft tissues. The roentgenologic appearance varied; occasionally the femur showed a local symmetrical expansion and thinning of the cortex; in 4 there was an associated pathologic fracture (Fig. 31). In some instances the bone was not expanded and the radiolucent area was sur-

of the skeleton was normal. A tentative diagnosis of eosinophilic granuloma of bone was offered, after which the diseased area was thoroughly curetted. Histologically the lesion was typical of fibrous dysplasia.

In the 8 cases involving the *tibia* the middle of the bone was more frequently affected than either end; in the latter region the position

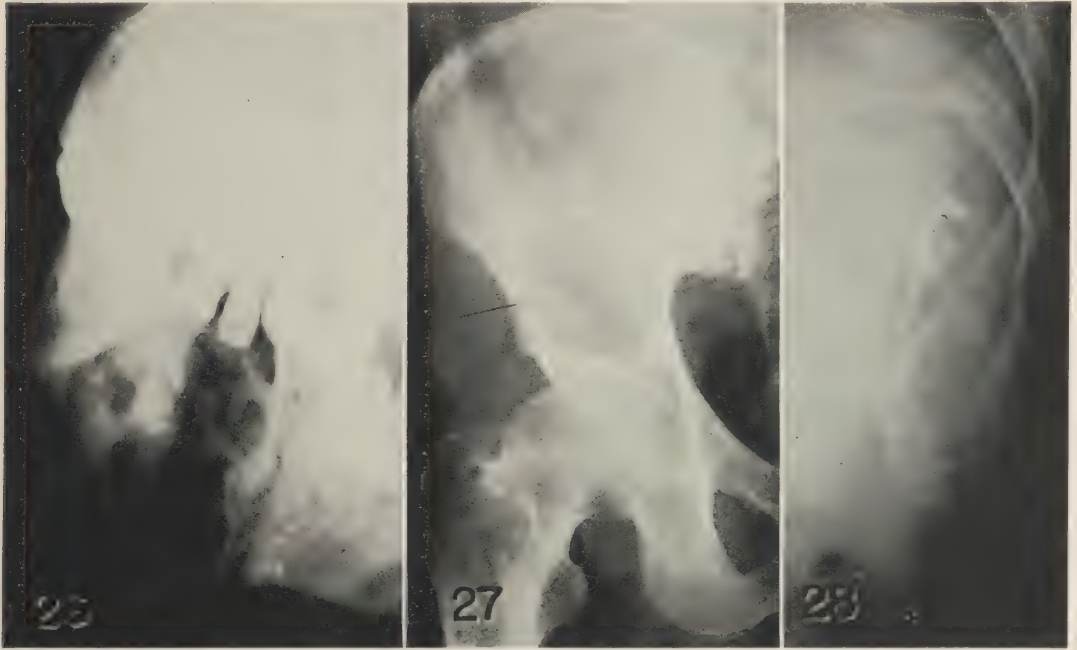


FIG. 26. Case 13. Area of fibrous dysplasia in the right half of the mandible.

FIG. 27. Case 16. A large radiolucent area in the right ilium. Biopsy had the appearance characteristic of fibrous dysplasia.

FIG. 28. Case 42. Fibrous dysplasia of the anterior posterior of the right 10th rib.

rounded by a layer of condensed bone (Fig. 1 and 2).

Case 50 gives a representative history. A 19-year-old white soldier first noticed pain and limitation of motion in his right knee. During the following month these symptoms became more severe and the patient was hospitalized. Physical examination was negative except for the presence of a diffuse tender bony mass in the left popliteal space and impaired flexion of the knee. The clinical diagnosis was chronic osteomyelitis of the distal end of the femur. The roentgenograms showed several "cystic" areas and subperiosteal new bone formation in the distal end of the femur. The remainder

was often eccentric (Fig. 3). Local swelling of the leg was present in 4 cases; a representative history follows.

Case 64. Three and a half years ago, when the patient was 20 years old, he fell and struck his knee against a board. Shortly thereafter he noticed a swelling at the upper end of the right tibia associated with an aching pain. Physical examination revealed a firm, slightly tender mass measuring 5.0 x 3.7 cm. just below the anterior aspect of the knee. A roentgenogram showed a large irregular area of decreased density lateral to the midline, in the proximal metaphysis of the tibia. There was thinning and expansion of the cortex as

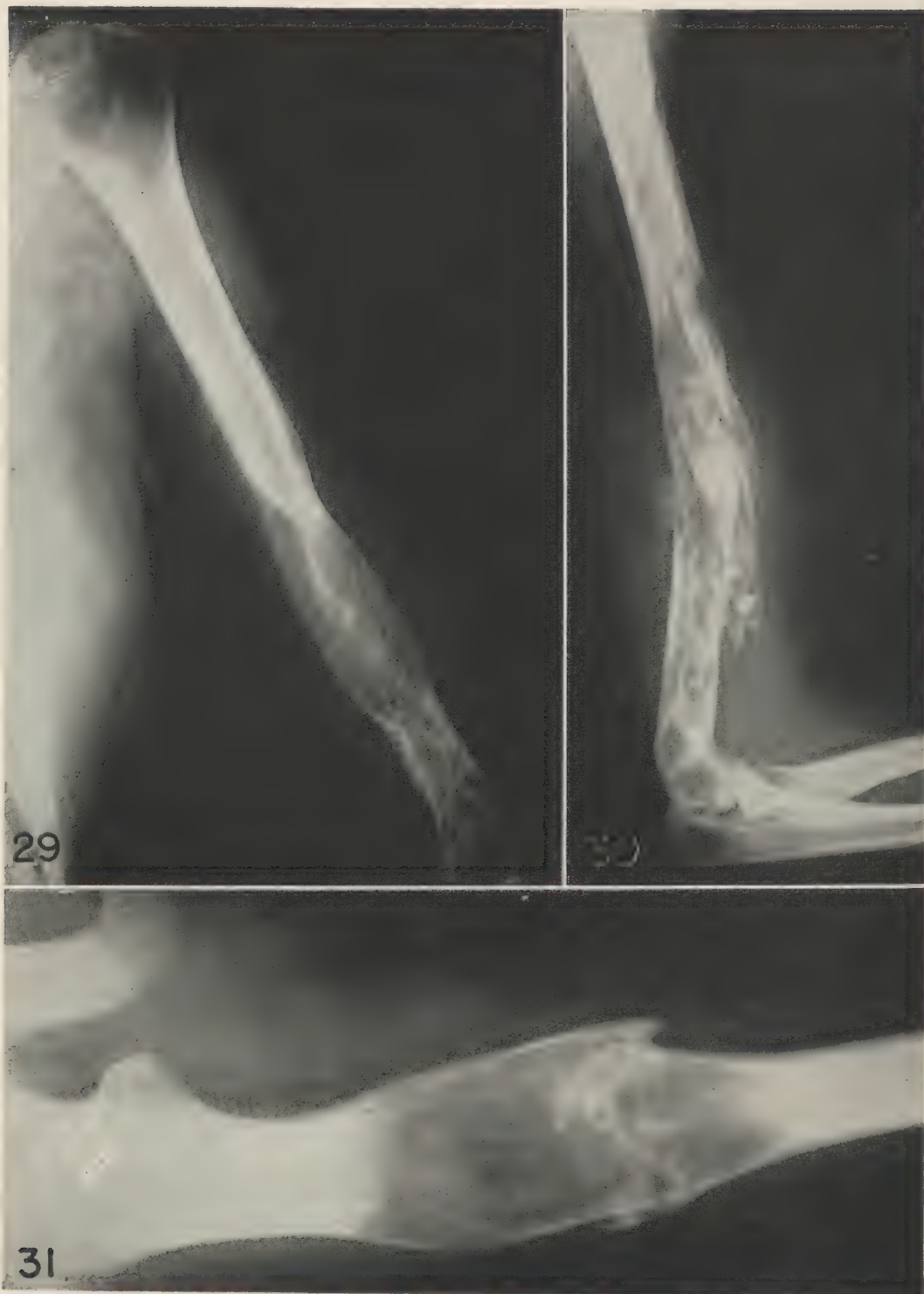


FIG. 29. Case 47. Fibrous dysplasia of the distal half of the left humerus. The cortex is greatly thinned and expanded.

FIG. 30. Case 47. Pathologic fracture of the humerus which was incurred two weeks after taking the roentgenograms in figure 29.

FIG. 31. Case 56. Fibrous dysplasia in the shaft of the right femur. Onset of symptoms with pathologic fracture.

well as condensation of the adjacent cancellous bone. The rest of the skeleton was normal. The roentgen diagnosis was chondroma, giant cell tumor, or nonosteogenic fibroma.

Only a single instance (Case 67, Table 4) of involvement of the *fibula* (Fig. 4) appeared in the series. The condition was diagnosed on roentgenologic evidence as an enchondroma. A pathologic fracture occurred while the patient was under observation; histologically the lesions presented no unusual features.

DISCUSSION

We shall now consider, first, the relationship of fibrous dysplasia to certain other conditions, namely, von Recklinghausen's neurofibromatosis, ossifying fibroma of bone, and nonosteogenic fibroma of bone; second, the part played by trauma in the production of fibrous dysplasia, and third, the connection between the monostotic and polyostotic forms of fibrous dysplasia.

Von Recklinghausen's Neurofibromatosis: Thannhauser¹¹ believes that the connective tissue pattern of fibrous dysplasia resembles that of neurofibroma and would therefore identify the lesions, particularly the polyostotic form, with von Recklinghausen's neurofibromatosis. However, the Bodian stain, employed on many of our sections, failed to reveal any nerve fibers. The significance of this finding in casting doubt on the nervous origin of the connective tissue is heightened by the results obtained by McNairy and Montgomery¹² who studied neurofibromas from 15 typical cases of von Recklinghausen's neurofibromatosis employing the Bodian stain. They were able to demonstrate non-medullated nerve fibers in 12. Furthermore, the great variability in the connective tissue pattern found in different regions of the same section is unfavorable to Thannhauser's hypothesis.

Ossifying Fibroma: Several cases of fibrous dysplasia of the maxilla in our series were diagnosed by the pathologists who submitted them as ossifying fibromas. However, it is becoming increasingly clear that the lesions of the maxilla and mandible which have been

so diagnosed are really variants of fibrous dysplasia, as first suggested by Lichtenstein.⁵ He pointed out the identity of the histologic picture of ossifying fibroma of the maxilla with that of fibrous dysplasia in other bones. Mallory¹³ has accepted this interpretation, which is also supported by clinicoroentgenologic evidence. Nevertheless, the recognition that these conditions are identical is not widespread¹⁴ and needs to be emphasized. It is true that at first glance the spherical islets of osteoid or new bone frequently found in the maxillary lesions (Fig. 14) may appear quite different from those seen, for example, in lesions of the ribs (Fig. 11). However, such spherical structures are often associated with the elongate "typical" bone trabeculae of fibrous dysplasia in other bones. Furthermore, lesions of the maxilla, that clinically and on gross pathologic examination are identical with what has been called ossifying fibroma, may on histologic examination reveal a structure indistinguishable from that of fibrous dysplasia (Fig. 32). Stages intermediate between the trabecular and spherule type of bone formation are also encountered (Fig. 33). Careful comparison of the histopathologic picture of so-called ossifying fibroma with that of fibrous dysplasia has convinced us that the former is a variant of the latter, and not a separate disease entity.

Nonosteogenic Fibroma: In the files of the Army Institute of Pathology are 12 cases classified as nonosteogenic fibroma of bone. The lesion was located in the distal metaphysis of the femur 7 times, in that of the tibia 3 times, and once in the proximal metaphysis of the tibia and fibula respectively. Roentgenologically these lesions could not be distinguished from monostotic fibrous dysplasia, since the characteristic eccentric position of the former, stressed by Jaffé and Lichtenstein,¹⁵ was also found in proved cases of fibrous dysplasia. On the other hand, several of the so-called non-osteogenic fibromas were centrally located.

According to Jaffé and Lichtenstein the essential histologic characteristic of nonosteogenic fibroma is the absence of metaplastic bone. However, the sections from three of the

12 cases at the Institute showed trabeculae of osteoid and new bone (Fig. 34). In all cases the connective tissue pattern was identical with that of fibrous dysplasia. Lipoid cells, another distinguishing though not constant feature of nonosteogenic fibroma, were present in several typical cases of fibrous dysplasia in the present series. Similarly giant cells are readily found in both conditions. Since, there-

bone cysts, one is reluctant to suggest the possibility of injury as a factor in the production of monostotic fibrous dysplasia. Nevertheless there is some evidence in its favor. The high incidence of rib involvement may be linked to the exposed position of these bones, which makes them particularly liable to injury. A history of trauma is present in almost one third of our cases with rib lesions. However,

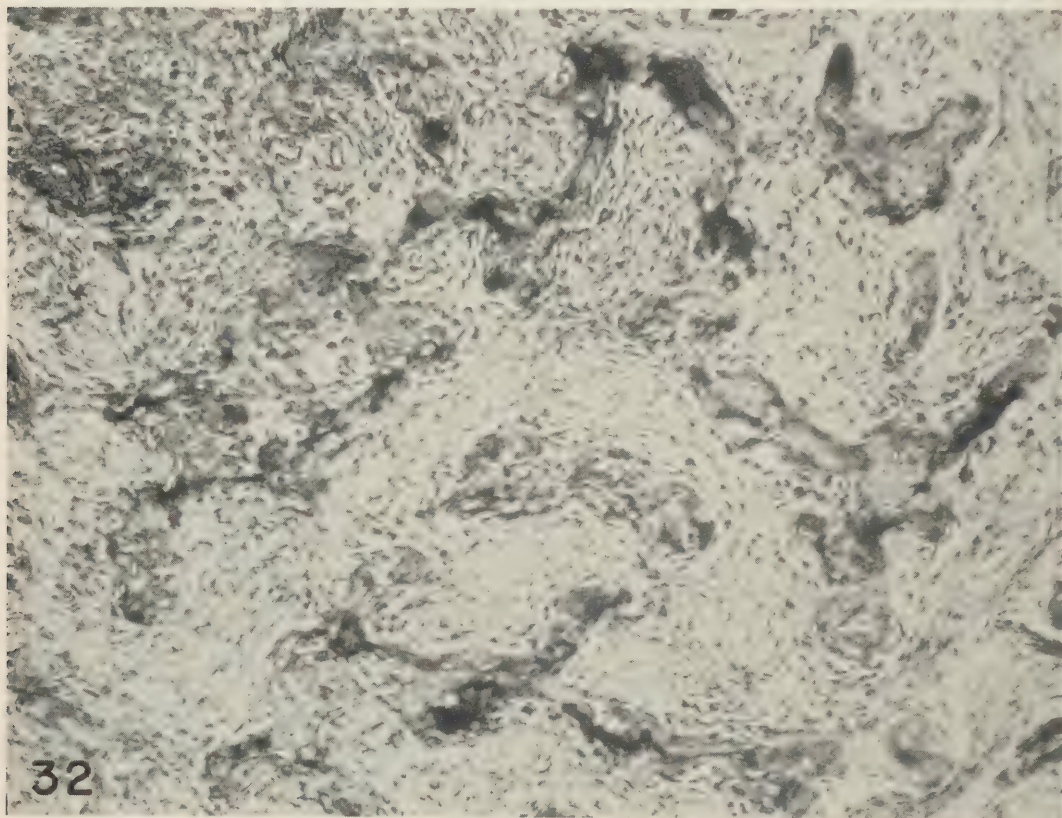


FIG. 32. Case 6. Section of a mass in the left maxilla previously identified as an ossifying fibroma. The characteristic histologic appearance of fibrous dysplasia is apparent. Compare with figure 11. Masson's trichrome stain. $\times 230$.

fore, we find no definite clinical, roentgenologic, or morphologic criteria by which non-osteogenic fibroma of bone and monostotic fibrous dysplasia may be distinguished, we regard the former as a variant of fibrous dysplasia.

Relation of Trauma to Fibrous Dysplasia: After the century old debate centering about the relationship of trauma to bone tumors, particularly of the giant cell variety, and to

in none is there proof that the fibrous dysplasia did not exist prior to the injury.

Such evidence, however, is presented in a case reported by Zenker,¹⁸ a roentgenogram of the chest having been taken at the time of injury. The patient was a 37-year-old white male who suffered a fracture of the right 8th and 9th ribs in the posterior axillary line while engaged in felling trees. The fractures were demonstrated by roentgenologic examination.

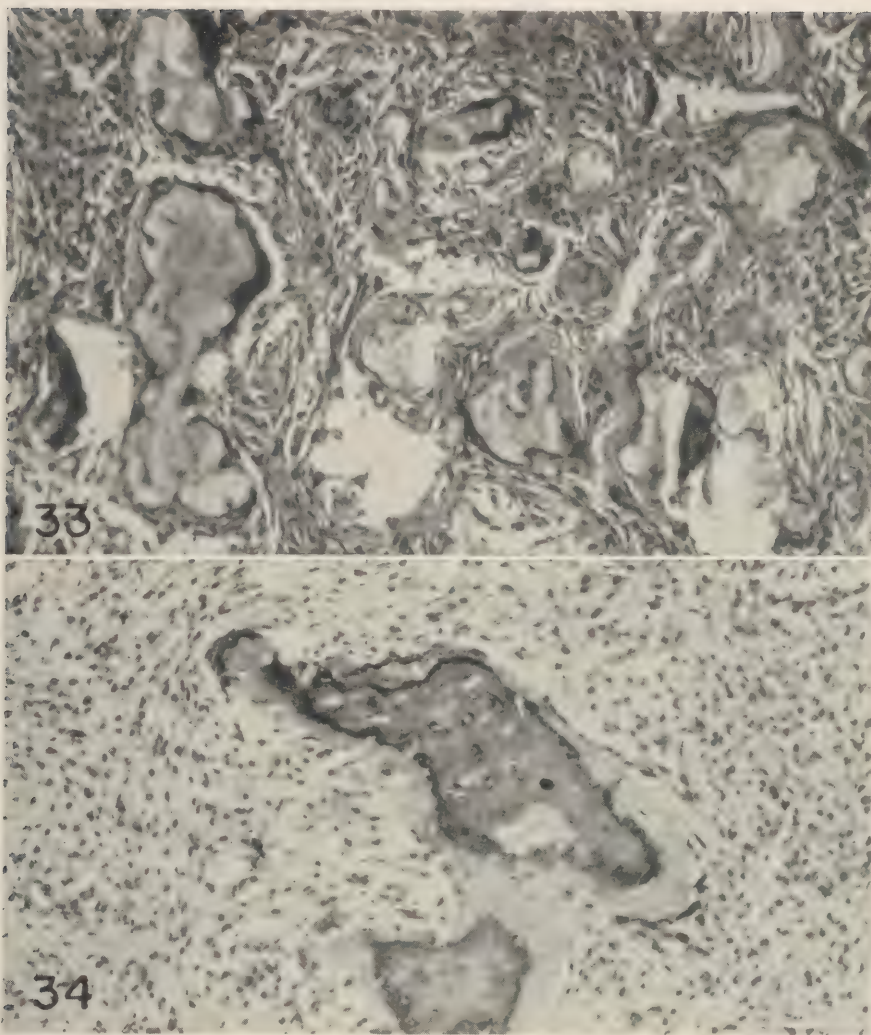


FIG. 33. Case 9. Irregular islets of partly calcified osteoid in loose connective tissue from a growth in the right maxilla. This histologic appearance is intermediate between the "typical" fibrous dysplasia of the preceding case and that shown in figure 14. All three, however, are examples of fibrous dysplasia. Hematoxylin and eosin stain. $\times 230$.

FIG. 34. A.I.P. Acc. 132175. Section of a lesion in the distal end of the left femur. The clinical and roentgenologic findings were compatible with nonosteogenic fibroma of bone. Microscopically lipoid cells and hemosiderin laden macrophages were abundant, however, widely scattered spicules of metaplastic bone were also present. In this case no sharp distinction can be made between fibrous dysplasia and nonosteogenic fibroma of bone.

Following treatment the patient was able to resume work 6 weeks after the accident. However, he complained of intermittent "rheumatic pains" in the right chest which ultimately led to another examination of the chest 10 years after the initial injury. At this time evidence of a healed fracture of the 8th rib was seen in roentgenogram. Below the site of the old

fracture the 9th rib was irregularly expanded by a "cystic tumor mass" which extended posteriorly from the axillary line for a distance of 15 cm. The roentgenogram and microphotographs leave no room for doubt that the lesions were an example of monostotic fibrous dysplasia.

In recent years it has been recognized that

fracture of the ribs may occur without external trauma. These fractures may be the result of opposing muscular tensions associated with cough, as in the 18 cases found by Harvey¹⁷ among 500 soldiers ill with virus pneumonia, or the 21 cases among approximately 3000 tuberculous patients reported by Oechsli.¹⁸ Fatigue fractures of the ribs following prolonged unaccustomed muscular activity such as that to which Army recruits may be subjected were described by Matthes and Thelen.¹⁹

The manner in which complete or partial fracture of a bone may act to produce fibrous dysplasia is admittedly unclear. Since this lesion often very closely resembles normal callus, one might compare it with the keloid formation that sometimes follows healing of a superficial injury. One of the most ardent proponents of the causative relationship between trauma and proliferative lesions of bone is Konjetzny. In a recent article²⁰ he considered this in relation to what he called localized osteitis fibrosa and expressed the belief that a correlation did exist. Only twice in our series was there a history of trauma associated with monostotic fibrous dysplasia in the bones of the lower extremity: once the lesion occurred in a femur (Case 57) and once in a tibia (Case 64). However, those who would seek for a pre-existing injury to account for the appearance of fibrous dysplasia in a bone may call upon the occurrence of fatigue (march) fractures in these bones. The sites of fibrous dysplasia in the tibia and femur correspond well with those of fatigue fractures in these bones as recently reported by Leveton.²¹ An obstacle to the acceptance of this thesis, however, is the well known fact that the overwhelming number of fatigue fractures occur in the metatarsal bones;²² whereas, these were never the seat of fibrous dysplasia in the series here reported.

The possible relation of injury to local fibrosis in the metaphysis of the long bones is supported in a report by Hatcher.²³ This author believes that the lesion identified by Jaffé and Lichtenstein¹⁵ as nonosteogenic fibroma of bone is not a true tumor. Hatcher

frequently found it in association with an epiphysal disorder due to altered blood supply, and suggests that the fibrous lesions of the metaphysis may be due to a similar vascular derangement.

In sum, there is a considerable body of evidence which links monostotic fibrous dysplasia with previous trauma, but the significance of this factor cannot as yet be evaluated with certainty.

Relation of the Monostotic to the Polyostotic Form of Fibrous Dysplasia: In the 67 cases of monostotic fibrous dysplasia comprising the present series, there were no recognizable congenital anomalies in the bones or other organs, and excessive cutaneous pigmentation was absent—findings which are characteristic of the polyostotic form. Our cases therefore do not support the belief that polyostotic, and monostotic fibrous dysplasia are different stages of the same disease entity. Rather, it may be that the bone lesions of both varieties are secondary to the action of widely different etiologic factors. Thus the polyostotic lesions found in young girls affected with precocious puberty may be related to the associated high estrogen content of the blood acting through the parathyroids, as suggested by Bremer²⁴ and recently supported by Scholder.²⁵ Different endocrine disturbances may be responsible for the multiple bone lesions when they occur in men or in women with normal secondary sexual characteristics.

A variety of etiologic factors may produce the solitary form of fibrous dysplasia. From a study of the cases in this series it seems probable that many represent an abnormal response to injury. Nothing in the history of our cases suggests that the lesions are manifestations of a congenital fault. There is no support for the identification of monostotic fibrous dysplasia as a hamartoma, a term employed by certain investigators of this disease.⁶ It should be remembered that this term was introduced by Albrecht²⁶ and defined as a tumor-like structure in which there is evidence only of an abnormal mixture of the normal tissue elements of the organ in which it occurs. Since the metaplastic forma-

tion of bone and cartilage by the medullary connective tissue is a normal occurrence following bone fracture, and because this same transformation of connective tissue into bone is frequently found elsewhere in the body, the identity of fibrous dysplasia with hamartoma seems unlikely.

SUMMARY

1. During the war the Army Institute of Pathology received tissue and records of 69 cases of fibrous dysplasia that had occurred in Army personnel. Of these 67 were monostotic and in only 2 were several bones affected.

2. Remarkable in this series was the frequency of rib involvement. Of the 29 rib lesions, 12 were incidental findings on routine chest films.

3. Evidence is presented which suggests that so-called ossifying fibroma and non-osteogenic fibroma of bone are variants of fibrous dysplasia.

4. The monostotic form of fibrous dysplasia is not a congenital anomaly, and etiologically has probably nothing in common with the form of polyostotic fibrous dysplasia found in Albright's syndrome. It may represent a disturbance of the normal reparative processes following any of a variety of bone injuries.

REFERENCES

- ¹ Schmorl, G.: Ueber Ostitis deformans, Paget. *Virch. Arch. f. path. Anat.* 283: 694-751, 1932.
- ² Weil, A.: Pubertas praecox und Knochenbrüchigkeit. *Klin. Wchnschrft. Pt. 2*: 2114-2115, 1922.
- ³ McCune, D. S., and Bruch, H.: Osteodystrophia fibrosa. *Am. J. Dis. Child.* 54: 806-848, 1937.
- ⁴ Albright, F., Butler, A. M., Hampton, A. O., and Smith, P.: Syndrome characterized by osteitis fibrosa disseminata, areas of pigmentation and endocrine dysfunction, with precocious puberty in females. *New England J. Med.* 216:727-746, 1937.
- ⁵ Lichtenstein, L.: Polyostotic fibrous dysplasia. *Arch. Surg.* 36: 874-898, 1938.
- ⁶ Lichtenstein, L., and Jaffé, H. L.: Fibrous dysplasia of bone. *Arch. Path.* 33: 777-816, 1942.
- ⁷ Weidenreich, F.: Das Knochengewebe. *Handb. d. mikr. Anat. d. Mensch.* 2 pt 2, 391-520. Berlin, Julius Springer, 1930.
- ⁸ Leriche, R., and Policard, A.: *The Normal and Pathological Physiology of Bone*. St. Louis, Mosby, 1928.
- ⁹ Pugh, D. G.: Fibrous dysplasia of the skull: a probable explanation for leontiasis ossea. *Radiology.* 44: 548-555, 1945.
- ¹⁰ Falconer, M. A., Cope, C. L. and Robb-Smith, A. H. T.: Fibrous dysplasia of bone with endocrine disorders and cutaneous pigmentation. (Albright's Disease). *Quart. J. Med.* 11: 121-154, 1942.
- ¹¹ Thannhauser, S. J.: Neurofibromatosis (von Recklinghausen) and osteitis fibrosa cystica localisata et disseminata (von Recklinghausen). *Medicine.* 23: 105-149, 1944.
- ¹² McNairy, J. D., and Montgomery, H.: Cutaneous tumors of von Recklinghausen's disease (neurofibromatosis). Report of a histologic study, with special reference to nerve fibers and the Bodian stain. *Arch. Dermat. & Syph.* 51:384-390, 1945.
- ¹³ Mallory, T. B.: Pathology: Diseases of bone. *New England J. Med.* 227:955-960, 1942.
- ¹⁴ Hara, H. J.: Ossifying fibroma of the superior maxilla. *Arch. Otolaryng.* 40: 180-188, 1944.
- ¹⁵ Jaffé, H. L., and Lichtenstein, L.: Non-osteogenic fibroma of bone. *Am. J. Path.* 18: 205-221, 1942.
- ¹⁶ Zenker, R.: Zur Frage der traumatischen Entstehung der Ostitis fibrosa localisata. *Beitr. z. path. Anat. u. allg. Path.* 103: 451-56, 1939.
- ¹⁷ Harvey, R. M.: Rib fractures in atypical pneumonia. *Am. J. Roent. & Rad. Ther.* 52:487-493, 1944.
- ¹⁸ Oechsli, W. R.: Rib fractures from cough. *J. Thoracic Surg.* 5:530-534, 1935-36.
- ¹⁹ Matthes, H. G., and Thelen, A.: Ermüdungsbrüche der Rippen mit typischer Lokalisation. *Chirurg.* 11:537-542, 1939.
- ²⁰ Konjetzny, G. E.: Sogenannte lokalisierte Ostitis fibrosa und Trauma. *Monatschrift f. Unfallh.* 46: 572-577, 1939.
- ²¹ Leveton, A. L.: March (fatigue) fractures of the long bones of the lower extremity and pelvis. *Am. J. Surg.* 71: 222-232, 1946.
- ²² Hartley, J. B.: "Stress" or "fatigue" fractures of bone. *Brit. J. Radiol.* 16: 255-262, 1943.
- ²³ Hatcher, C. H.: The pathogenesis of localized fibrous lesions in the metaphyses of long bones. *Ann. Surg.* 122: 1016-1030, 1945.
- ²⁴ Bremer, J. L.: Osteitis fibrosa localisata: an experimental study. *Arch. Path.* 32: 200-210, 1941.
- ²⁵ Scholder, B. M.: The syndrome of precocious puberty, fibrocystic bone disease, and pigmentation of the skin: 11 years observation of a case. *Ann. Int. Med.* 22: 105-118, 1945.
- ²⁶ Albrecht, E.: Ueber Hamartome. *Verhandl. d. deutsch. path. Gessell.* 7: 153-157, 1904.

BRONCHIAL ADENOMAS*

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(With eighteen illustrations)

BRONCHIAL ADENOMA

THE antemortem recognition of bronchial adenoma has increased steadily since the reports of Kramer¹ in 1930 and Wessler and Rabin² in 1932. Earlier diagnosis of a larger number of cases has resulted from a growing awareness that cough, hemoptysis and other pulmonary symptoms often demand more extensive investigation than roentgenologic examination of the chest. Bronchoscopy and biopsy are indispensable adjuncts.

Bronchial adenomas constitute approximately 8 to 10 per cent of all primary bronchopulmonary neoplasms. They usually occur in the third and fourth decades, that is, in the age group which includes the majority of the military personnel; hence they have been encountered with relative frequency in the larger Army hospitals. The favorable outcome to be anticipated in these cases is in decided contrast to the grave prognosis offered victims of bronchogenic carcinoma, but early differential diagnosis is essential for their proper treatment.

This study is based upon records and specimens from 39 cases at the Army Institute of Pathology. It includes an account of the clinical features, the morphology of the neoplasms, and the results of treatment. Fourteen of the tumors were found in civilians and 25 in military personnel. The relevant data have been summarized in Table 1. Three cases have been reported previously.^{3,4,5}

Since the recognition of this tumor as an entity, it has been given many names: poly-poid adenoma,⁶ basal cell carcinoma,⁷ adenomatous polyp,⁸ benign glandular bronchogenic tumor,⁹ vascular adenoma,¹⁰ carcinoid and cylindroma,¹¹ mixed tumor,¹² malignant ade-

noma,¹³ and anlage and rest tumor.¹⁴ As pointed out by Mallory,¹⁵ the term bronchial adenoma is not accurately descriptive, for the most common type rarely forms glands, and its origin is still in doubt; yet the name is so widely used and its implications are so well understood that its retention seems advisable.

LITERATURE

Many excellent reviews of the literature relating to the various aspects of bronchial adenoma have appeared within recent years. The reports of Womack and Graham,¹² Goldman and Stephens,¹⁶ Brunn and Goldman,¹⁷ Foster-Carter,¹⁸ Anderson,¹⁹ Stout,²⁰ Laff and Neuburger,²¹ and Riordan and Richards²² have included most of the papers on the subject published prior to 1944. The most recent contributions are those of Nager,²³ Jackson, Konzelmann and Norris,²⁴ Graham and Womack,²⁵ Chamberlain and Gordon,²⁶ Harris,²⁷ and Moersch, Tinney and McDonald.^{28,29} In all, over 250 cases have been recorded.

REPRESENTATIVE CASES

Seven of the 39 cases have been selected to illustrate various clinical and pathologic features of bronchial adenoma.

Case 9. AIP. Acc. No. 84528:

A white male, 27 years old, had an acute respiratory infection with pleurisy and slight effusion in 1941. In June 1942 he had another attack characterized by malaise, fever, cough, expectoration, dyspnea, and pain in the lower part of the right chest. Roentgenograms showed elevation of the right diaphragm and diffuse mottling at the base of the right lung. These changes persisted, although the acute illness subsided in 12 days. Bronchoscopy revealed a granular tumor which bled freely on contact and which had produced a narrowing of the right lower lobe bronchus. The

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† Nassau County Sanatorium, Farmingdale, New York.

patient died during bronchoscopy 1 year and 5 months after the onset of symptoms. Autopsy was not performed, the histologic description being based on biopsy material.

Pathologic Findings: The bronchial epithelium which covered the tumor had undergone squamous metaplasia and was separated from it by a narrow band of connective tissue. The tumor cells were epithelial, medium-sized, usually polygonal, with pale, finely granular cytoplasm, and round or oval, slightly hyperchromatic nuclei. Mitoses were not seen. The cells were arranged in cords and nests that simulated the pattern and morphology of appendiceal carcinoids. The stroma consisted largely of bone, though in one area there were hyalinized bundles of connective tissue that resembled the matrix of a mixed tumor. The final diagnosis was bronchial adenoma, carcinoid type.

Case 10. AIP. Acc. No. 84794:

A white male, 35 years of age, had had pneumonia in 1936. An acute pulmonary infection in June 1942 was accompanied by cough and expectoration of dark blood. Symptoms subsided after 20 days, although the cough persisted with a small amount of sputum but no blood. Roentgenograms showed a round mass, 4 cm. in diameter, in the left pulmonary hilus, and an area of increased density extending from the hilus to the left base. These changes were interpreted as a tumor of the left lower lobe with atelectasis. The diagnosis made from bronchoscopic biopsy specimens was bronchial adenoma. Lobectomy was advised but refused.

The patient continued to work for almost 2 years, but he tired easily, had a chronic cough, and occasionally expectorated blood-streaked sputum. Periodic roentgenograms of the chest showed gradual enlargement of the tumor. Left lower lobectomy was performed in October 1944, and the patient was discharged from the hospital in February 1945 after the subsidence of postoperative pleural effusion. Subsequent follow-up data were not available.

Pathologic Findings: A soft, well-circum-

scribed neoplasm measuring 5 x 5 x 3.5 cm. was found embedded in the wall of a large bronchus. A pedunculated extension of the tumor filled the bronchus for a distance of 5 cm. The distal bronchi were dilated.

At microscopic examination it was seen that the portion of the tumor which protruded into the bronchus was covered by cuboidal and respiratory epithelium. Beneath this was a thin layer of compressed fibrous tissue, infiltrated by tumor cells. The bulk of the intramural tumor formed a fairly well circumscribed lesion that surrounded the bronchial cartilages and displaced the remaining normal structures. At the periphery of the main mass were small nests of infiltrating tumor cells.

The cells in some regions of the neoplasm were arranged in cords reminiscent of appendiceal carcinoids. Here and elsewhere in the tumor they were epithelial in character, with scanty polychromatic and finely granular cytoplasm. The nuclei, though usually uniform, were occasionally variable in size and chromatin content; nucleoli were rarely seen; mitoses were absent. The Fontana stain showed silver-positive intracellular granules in the biopsy specimen, although the same stain failed to demonstrate them in the main portion of the tumor. The connective tissue stroma was scanty and moderately vascular. The lung parenchyma was partially atelectatic but not significantly inflamed. The final diagnosis was bronchial adenoma, carcinoid type.

Case 12. AIP. Acc. No. 86741:

A white male, 38 years of age, entered a hospital in November 1942 with a history of persistent cough and hemoptysis following pneumonia. Roentgenograms showed atelectasis of the right lower lobe, where a tumor was subsequently demonstrated by bronchoscopy. The first diagnosis on the tissue from biopsy was bronchogenic carcinoma, but after further study this was changed to bronchial adenoma. A right lower lobectomy was performed in December 1942. The patient was transferred to another hospital from which he was discharged in September 1943. There was no evidence of recurrence at that time.

Pathologic Findings: At the hilus the orifice of the lower lobe bronchus was filled with an encapsulated tumor, 4 cm. in diameter, that had its origin in the bronchial wall. Its cut surface was tan and homogeneous.

Microscopic examination showed that the tumor was separated from the lumen of the bronchus by respiratory epithelium and associated, partly calcified, connective tissue. Incorporated in the tumor were nerves, bronchial cartilages, glands, and ducts; peripherally, tumor cells infiltrated the bronchial wall. Some of the incorporated cartilages were undergoing ossification. Although a few spicules of bone were found free in the tumor, they were always near bronchial cartilage. Some of the bone contained normal marrow, but elsewhere neoplastic cells filled the spaces between the spicules. The tumor cells were epithelial in character with pale, finely granular cytoplasm and round to oval, medium-sized nuclei containing a moderate amount of chromatin. Mitoses were not observed. The cells were arranged in cords and nests separated by delicate fibrous strands or dense collagenous bundles. Some of the latter contained calcium granules. The pattern was indistinguishable from that of the appendiceal carcinoids. There were a few pseudoglands, the central spaces of which were formed by small capillaries and their surrounding connective tissue. Nests of neoplastic cells were found in the capsule of a peribronchial lymph node. The final diagnosis was bronchial adenoma, carcinoid type.

Case 15. AIP. Acc. No. 94639:

A white male, 28 years old, first had hemoptysis accompanied by cough and expectoration in 1930. Between then and 1937 he had three attacks of pneumonia. His cough increased; he lost weight and became weak. In 1937 roentgenograms revealed atelectasis of the left lung; tissue removed from the left main bronchus was diagnosed adenoma. Additional specimens examined during the next 4 years were similarly classified. The patient was fairly well until February 1943 when he had scarlet fever complicated by renal in-

sufficiency. At that time roentgenograms showed the trachea and mediastinum shifted to the left and the left lung still atelectatic. The patient died in uremia 28 days after the onset of the scarlet fever and 13 years after the first symptoms of the bronchial adenoma.

Pathologic Findings: At autopsy the heart and mediastinum were displaced to the left; the left pleural space was obliterated by dense fibrous adhesions. The left lung weighed 850 gm., showed extensive fibrosis, and in its lower lobe was bronchiectatic. The bronchi were patent and presented no evidence of tumor. In the left upper lobe was a thick-walled cavity, 3 cm. in diameter. One hilus lymph node measured 3 x 2 x 2 cm. and had a "fish flesh" appearance. The spleen, liver and kidneys were enlarged due to the deposition of amyloid.

At microscopic examination it was found that the hilus lymph node was almost wholly replaced by a metastatic tumor. The neoplastic cells were arranged in interlacing cords separated by moderately vascular connective tissue. The structure and arrangement of the cells were similar to those observed in the biopsy tissue obtained in 1937, 1938 and 1941, which resembled appendiceal carcinoid. Final diagnosis was bronchial adenoma, carcinoid type, metastatic in a hilus lymph node.

Case 31. AIP. Acc. No. 80340:

A white female, 37 years of age, first had fever, cough and signs of right middle and upper lobe pneumonia in 1933. Roentgenograms disclosed a slowly resolving infiltration in the right upper lobe and a nodular shadow in the right hilus. Subsequently hemoptysis occurred with menstruation several times. After X-ray therapy the nodule appeared to regress but became more prominent in 1942, although no abnormality was noted at bronchoscopy. X-ray therapy was administered again in November 1942. In August 1943, the patient complained of cough and occasional hemoptysis. Two months later a right middle and upper lobectomy was performed. The pathologic diagnosis was adenoma of the right upper lobe bronchus with

questionable malignancy. The patient was well until November 1945 when a laparotomy for suspected ectopic pregnancy revealed several tumor nodules, 5 mm. to 5 cm. in diameter in the liver, but no ectopic pregnancy. The appendix was removed and also the uterus which contained fibroleiomyomas.

Pathologic Findings: Microscopic examination of tissue from the lobe removed at operation showed the tumor to be separated from the bronchial lumen by squamous epithelium and an underlying zone of collagenous fibrous tissue. It was composed of epithelial cells arranged in cords and irregular masses separated by a moderate amount of connective tissue. The cytoplasm of the tumor cells was faintly polychromatic and granular; the nuclei were round or oval and moderately hyperchromatic. Mitoses were not seen. A few spicules of bone in the periphery of the tumor represented ossified bronchial cartilages.

The neoplastic tissue from the liver was made up of the same type of cells, but the cords and masses in which they were arranged were less well defined than in the primary tumor. The cell structure and arrangement of both the bronchogenic tumor and the hepatic metastasis were consistent with those of carcinoid. There was no evidence of carcinoid in the appendix.

The final diagnosis was bronchial adenoma, carcinoid type, metastatic in the liver.

These five cases represent the same type of bronchial adenoma. In Case 10, the unusual nuclear pleomorphism was considered insufficient for an unequivocal diagnosis of malignancy. Case 25 (Table 1) showed a similar variation but was classified as an adenoma.

Case 35. AIP. Acc. No. 73373:

A white woman, 37 years old in 1940, had suffered from mild thoracic pain for the previous year. A routine roentgenogram of the chest made in August 1935 had been normal; another in 1938 had shown a rounded density, 1 cm. in diameter, in the lower lobe of the left lung near the hilus; this shadow appeared much larger in June 1940. A few months later a left lower lobectomy was per-

formed. There was evidence of recurrence 5 years after operation.

Pathologic Findings: A well circumscribed 4.5 x 4 x 4 cm. tumor was present 2 cm. from the hilus and 0.5 cm. beneath the pleura. Its cut surface was grayish white, the center streaked with yellow.

Microscopically it was seen that the tumor arose in the bronchial wall, surrounded the cartilages, and filled several pulmonary alveoli. It was composed of irregular masses of small, deeply stained, spindle-shaped cells with scant cytoplasm. The nuclei were small and hyperchromatic. Throughout the lesion were nests of concentrically arranged cells that were partially keratinized or calcified and bore a resemblance to Hassall's corpuscles. All stages of transition from the typical tumor cells to the keratinized nodules were demonstrable. The stroma was scant in some areas, whereas elsewhere there were prominent bundles of collagenous connective tissue.

Frequently the periphery of the cell nests showed palisading similar to that observed in basal cell carcinomas of the skin. In other areas there were small spaces containing an amorphous precipitate which failed to stain with mucicarmine. These portions of the tumor were like some of the mixed tumors of salivary glands and also resembled epithelioma adenoides cysticum.

Originally the tumor was classified as an epidermoid carcinoma, basal cell type. The final diagnosis was bronchial adenoma, mixed tumor type.

Case 37. AIP. Acc. No. 84802:

A white male, 28 years old, had pneumonia in March and again in April of 1942; these episodes were followed by a productive cough. Roentgenograms showed atelectasis of the right lower lobe, and bronchoscopic examinations in July 1942 revealed a polypoid tumor in the right lower lobe bronchus. The diagnosis following biopsy was bronchial adenoma. Additional specimens obtained in August 1942 were called low grade adenocarcinoma in one instance and adenofibroma in another. The right lung was removed during the following

TABLE I

Case No. & Accession No.	Sex	Age	Predominant Symptoms & Signs	Duration	Roentgenographic Changes	Location of Tumor	Biopsy Diagnosis	Method of Removal	Result after operation	Final Classification
*1 60845	F	44	Cough, sputum, chills, fever	1 yr.	Atelectasis, left lung	Left lower lobe	Adenoma, Adenomatous carcinoma	Bronchoscopy	Well, 4 yrs.	Carcinoid type
*2 74460	F	27	Pleurisy with effusion	10 mos.	Atelectasis, right lower lobe	Right lower lobe	Adenoma	Pneumonectomy	Well, 5 yrs. 8 mos.	Carcinoid type
3 74517	F	37	Fatigue, cough, fever	2 yrs. 5 mos.	Inflammatory infiltration. Lt. upper lobe	Left upper lobe	Adenoma	Bronchoscopy	Well, 4 yrs. 8 mos.	Carcinoid type
4 81971	M	23	Cough, expectoration Hemoptysis	3 yrs. 4 mos.	Inflammatory infiltration, Lt. lower lobe	Left main bronchus	Carcinoma	Pneumonectomy	Dyspnea, 3 yrs. 1 mo.	Carcinoid type
5 82034	F	32	Cough hemoptysis	6 mos.	Atelectasis Rt. lower lobe; mass, rt. hilus	Right lower lobe	Carcinoma	Pneumonectomy	Well, 9 yrs. 11 mos.	Carcinoid type
6 82037	F	45	Cough Hemoptysis	4 yrs. 3 mos.	Atelectasis, left upper lobe	Left upper lobe	Adenoma	Pneumonectomy	Well, 6 yrs. 8 mos.	Carcinoid type
*7 82038	F	37	Hemoptysis associated with menstruation	8 yrs.	Atelectasis left lung	Left main bronchus	Adenoma	Pneumonectomy	Well, 4 yrs. 11 mos.	Carcinoid type
8 82042	M	48	Recurrent respiratory infection	4 yrs. 3 mos.	Atelectasis, left lung	Left upper lobe	None	Pneumonectomy	Well, 3 yrs.	Carcinoid type
9 84528	M	27	Recurrent pleurisy	1 yr.	Atelectasis, right lower lobe	Right lower lobe	Endobronchial sarcoma	Bronchoscopy	Expired at bronchoscopy	Carcinoid type
10 84794	M	35	Cough Hemoptysis	3 yrs. 4 mos.	Mass near left hilus	Left lower lobe	Adenoma	Lobectomy	Well, 7 mos.	Carcinoid type
11 85956	M	21	Pain in right chest, cough	"several years"	Atelectasis, right lower lobe	Right lower lobe	Carcinoma Adenoma	Bronchoscopy	No follow-up	Carcinoid type
12 86741	M	38	Hemoptysis, pneumonia	Not known	Atelectasis, right lower lobe	Right lower lobe	Carcinoma Adenoma	Lobectomy	No follow-up	Carcinoid type
13 90469	M	21	Cough, dyspnea	8 mos.	Inflammatory infiltration Lt. lw. lobe	Left lower lobe	Adenoma	Bronchoscopy	Well, 7 mos.	Carcinoid type

14 90995	M	24	Hemoptysis	5 mos.	None	Left main bronchus	Adenoma	Bronchoscopy	Well, 2 yrs.	Carcinoid type
15 94639	M	28	Recurrent broncho-pneumonia hemoptysis	7 yrs.	Atelectasis left lung	Left main bronchus	Adenoma	Bronchoscopy	Expired 2 yrs. after last bronchoscopy	Carcinoid type
16 100862	F	30	Recurrent respiratory infection Hemoptysis	9 yrs. 5 mos.	Mass rt. hilus. Inflammatory infiltration, rt. base	Right lower lobe	None	Lobectomy	Well, 1 yr. 9 mos.	Carcinoid type
17 100866	M	19	"Atypical pneumonia"	4 mos.	Inflammatory infiltration, rt. lower lobe	Right lower lobe	Carcinoma	Pneumonectomy	No follow-up	Carcinoid type
18 102721	M	23	Not known	Not known	Not known	Right lower lobe	Adenoma	Bronchoscopy	No follow-up	Carcinoid type
19 103405	F	43	Hemoptysis	3 wks.	Atelectasis, left lung	Left lower lobe	Carcinoma	Pneumonectomy	Well, 1 yr. 10 mos.	Carcinoid type
20 103522	F	73	Tumor was incidental finding at autopsy after death from hypertension	—	—	Left upper lobe	—	—	—	Carcinoid type
21 105012	M	23	Recurrent fever, cough	4 mos.	Atelectasis, left upper lobe	Left upper lobe	Adenoma	Bronchoscopy	Well, 2 months	Carcinoid type
22 106993	M	35	Recurrent pneumonia	1 yr. 8 mos.	Atelectasis, rt. middle lobe	Right middle lobe	None	Lobectomy	Well, 1 yr. 9 mos.	Carcinoid type
23 109382	M	29	Recurrent cough, fever, wheeze	1 yr.	Inflammatory infiltration with lung abscess, lt. lw. lobe	Left lower lobe	Carcinoma Adenoma	Pneumonectomy	Well, 1 yr.	Carcinoid type
24 116096	M	37	Cough, Hemoptysis	11 yrs. 2 yrs.	Atelectasis right lower lobe	Right lower lobe	Adenoma	Lobectomy	Well, 3 mos.	Carcinoid type
25 117718	M	38	Cough, expectoration, Hemoptysis	5 yrs. 2 yrs.	Inflammatory infiltration, rt. lw. lobe	Right middle lobe	Carcinoma	Pneumonectomy	Expired after 28 days from empyema	Carcinoid type
26 118167	M	24	Recurrent respiratory infection	11 mos.	Atelectasis, left lower lobe	Left upper lobe	Adenoma	Pneumonectomy	Dyspnea, 1 yr. 3 mos.	Carcinoid type
27 118281	F	34	Hemoptysis	11 mos.	Atelectasis, inflammatory infiltration rt. lw. lobe	Right lower lobe	Adenoma	Lobectomy	Well, 4 mos.	Carcinoid type
28 120591	M	31	Cough, pain in right chest	Not known	Mass near right hilus	Right lower lobe	None	Lobectomy	Well, 5 mos.	Carcinoid type

TABLE I—(continued)

Case No. & Accession No.	Sex	Age	Predominant Symptoms & Signs	Duration	Roentgenographic Changes	Location of Tumor	Biopsy Diagnosis	Method of Removal	Result after operation	Final Classification
29 121943	M	25	Not known	Not known	Not known	Right lower lobe	Adenoma	Bronchoscopy	No follow-up	Carcinoid type
30 132719	M	48	Trauma, pain, left chest Hemoptysis	4 mos. 1 mo.	None	Left upper lobe	Carcinoma	Pneumonectomy	Well, 5 mos.	Carcinoid type
31 80340	F	37	Hemoptysis with menstruation	9 yrs.	Atelectasis, right middle & upper lobes	Right middle lobe	none	Lobectomy	Liver metastases after 2 yrs.	Carcinoid type
32 155988	M	22	None. Found at routine examination	Not known	Not known	Right lower lobe	Adenoma	Lobectomy	Well, 7 mos.	Carcinoid type
33 155198	F	35	Cough Acute respiratory infection	6 mos. 3 mos.	Atelectasis, right lower lobe	Right lower lobe	Carcinoma	Pneumonectomy	Well, 6 mos.	Carcinoid type
34 156546	M	24	Acute respiratory infection	9 mos.	Atelectasis, right lower lobe	Right lower lobe	Adenoma	Lobectomy	Well, 1 mo.	Carcinoid type
35 73373	F	37	Found at routine examination Pain in left chest	2 yrs. (before operation) 1 yr.	Mass near left hilus	Left lower lobe	None	Lobectomy	Recurred at 5 yrs.	Mixed tumor type
36 81914	F	35	Cough, dyspnea Hemoptysis	3 yrs. 2 yrs.	Masses, right hilus	Right lower lobe	Carcinoma	Bronchoscopy	Bloody pleural effusion; pleural nodules 3 yrs.	Mixed tumor type
37 84802	M	28	Chest pain Recurrent pneumonia	1 yr. 6 mos.	Atelectasis, inflammatory infiltration rt. lw. lobe	Right main bronchus	Adenoma Carcinoma Adenofibroma	Pneumonectomy	Well, 3 yrs. 6 mos.	Mixed tumor type
38 95277	M	38	Acute respiratory infection and slight weight loss	5 mos.	Inflammatory infiltration lt. lw. lobe	Left main bronchus	Carcinoma	Pneumonectomy	No follow-up	Mixed tumor type
39 112112	M	26	Cough, expectoration fever	11 yrs. 5 mos.	Atelectasis, right lower lobe	Right lower lobe	Cylindroma	Bronchoscopy	Bronchiectasis 10 mos.	Mixed tumor type

* Case 1 reported by Schwartz (4); Case 2 by Tyson & Milliken (5); Case 7 by Overholt (3).

October; convalescence was uneventful. Two years and three months after pneumonectomy there was no evidence of recurrence, and the patient was asymptomatic.

Pathologic Findings: A segment of the right main bronchus bore a smooth fusiform mass, measuring 1.7 x 1.3 x 1.2 cm., that bulged into the lumen and narrowed it to one half its normal diameter. The cut surface was tan after formalin fixation; several embedded bronchial cartilages were visible. The tumor had almost penetrated the bronchial wall. The

type of bronchial adenoma, for the cell pattern closely resembles that of certain mixed tumors of the salivary glands and epithelium adenoides cysticum, and is wholly different from the more frequently observed carcinoid variety.

CLINICAL AND PATHOLOGIC ANALYSES

Fourteen (36 per cent) of the tumors were in females, and 25 (64 per cent) were in males (Table 2). The neoplasm was discovered during life in all cases except one

TABLE 2
SEX AND AGE DISTRIBUTION BY YEARS

	Total	Under 20	20-29	30-39	40-49	50-59	60-69	70
Female	14	0	1	9	3	0	0	1
Male	25	1	14	8	2	0	0	0
	—	—	—	—	—	—	—	—
Total	39	1	15	17	5	0	0	1

greater part of the lung was atelectatic; the bronchi were not dilated.

Microscopic examination showed partial desquamation of the epithelium of the bronchial mucosa, but where present it was of squamous type and separated from the tumor by a zone of chronically inflamed fibrous tissue. The neoplastic cells extensively infiltrated the outer portion of the bronchial wall. In many regions the cells formed tortuous branching tubules; elsewhere they appeared as sharply outlined nests containing small spaces, some of which were filled with amorphous material, which did not stain with mucicarmine. The tumor cells were polygonal, had a scant amount of cytoplasm, and contained small, round or oval, hyperchromatic nuclei. Mitoses were not found. The connective tissue stroma presented no unusual features. The pattern assumed by the tumor cells was similar to that found in some mixed tumors of salivary glands and in epithelioma adenoides cysticum. The final diagnosis was bronchial adenoma, mixed-tumor type.

The last two cases represent a less common

(Case 20), in which a 6 mm. nodule of the carcinoid type was found after death from hypertensive heart disease. Seventy-one per cent of the females and 88 per cent of the males were between the ages of 20 and 40 years. The average age at onset of symptoms was 32 years in the women and 25 years in the men. The longest duration of symptoms among the women was 9 years and 5 months with an average of 3 years and 2 months; among the men it was 11 years and 5 months with an average of 2 years and 7 months.

Cough was a symptom in 66 per cent of cases; hemoptysis (including blood-streaking as well as severe hemorrhage) in 44 per cent; expectoration in 40 per cent; some form of chest pain, usually mild, in 36 per cent; fever in 36 per cent; dyspnea in 20 per cent; weight loss in 11 per cent, and wheeze in 9 per cent, (Table 3). Hemoptysis was concurrent with menstruation in two cases. Thirty-three per cent of the patients had had one or more attacks of acute pulmonary infection, apparently secondary to bronchial obstruction.

Clinical laboratory studies had no specific.

diagnostic significance.

Roentgenographically the tumor was demonstrable in 8 cases, atelectasis in 16, and inflammatory infiltration in 9 others. Figures 1, 2 and 3 illustrate these and other changes.

The affected bronchus was partially or completely obstructed in 19 cases, (Fig. 1 a). Bronchoscopic biopsy was performed in 34 cases resulting in immediate diagnosis of

At the last follow-up examinations of the remaining patients there was evidence of local recurrence in one (Case 35); hepatic metastases were found at laparotomy in another (Case 31). In case 36, with a mixed-tumor type of bronchial adenoma, no further attempt at removal was made after the original bronchoscopy. This patient had had partial collapse of the right lung and bloody pleural

TABLE 3
SUMMARY OF SYMPTOMS

	Cough	Hemop- tysis	Sputum	Fever	Pain	Dyspnea	Pleural Effusion	Weight Loss	Wheeze
Female	7	8	2	4	1	2	3	1	0
Male	18	8	12	9	12	5	3	3	3
Total	25	16	14	13	13	7	6	4	3

TABLE 4
LOCATION OF TUMORS

Right Lung					Left Lung			
Main Bronchus	Upper Lobe Bronchus	Middle Lobe Bronchus	Lower Lobe Bronchus	Total	Main Bronchus	Upper Lobe Bronchus	Lower Lobe Bronchus	Total
1	2	2	15	20	5	7	7	19

bronchial adenoma in 18; the same diagnosis after additional biopsy or review of the original sections in 5, carcinoma in 14, cylindroma in 1, and endobronchial sarcoma in 1.

The tumor was removed bronchoscopically in 9 cases. There were 11 lobectomies, with 2 lobes of the right lung removed in 2 instances. Pneumonectomy was performed in 15 cases.

Three of the 38 patients in whom the tumor was diagnosed during life have since died. One of these (Case 9) died during bronchoscopy 4 months after diagnosis. Another (Case 15) died of scarlet fever, amyloidosis, and subacute interstitial nephritis 2 years after the last bronchoscopic removal of tumor. The third death (Case 25) resulted from empyema 28 days after pneumonectomy; autopsy did not reveal any residual tumor,

effusion for 3 years. The last roentgenogram showed rounded pleural densities which might be interpreted as tumor nodules. The longest period of observation after operation was 10 years (Case 5). Nothing is known of 3 patients after the immediate postoperative period.

The tumor was located in the right lung in 20 cases and in the left in 19 (Table 4). The most frequent site was in the right lower lobe bronchus (15 cases). All of the tumors were located at or near the pulmonary hilus. They measured from 5 mm. in diameter to 5 x 5 x 3.5 cm. and were round and often polypoid with broad attachments to the bronchial walls (Figs. 4, 5 and 6). Some were soft; others were firm; their surfaces were smooth and pink to red. All of them were well demarcated grossly from the adjacent non-neoplastic tissue. Microscopic examina-

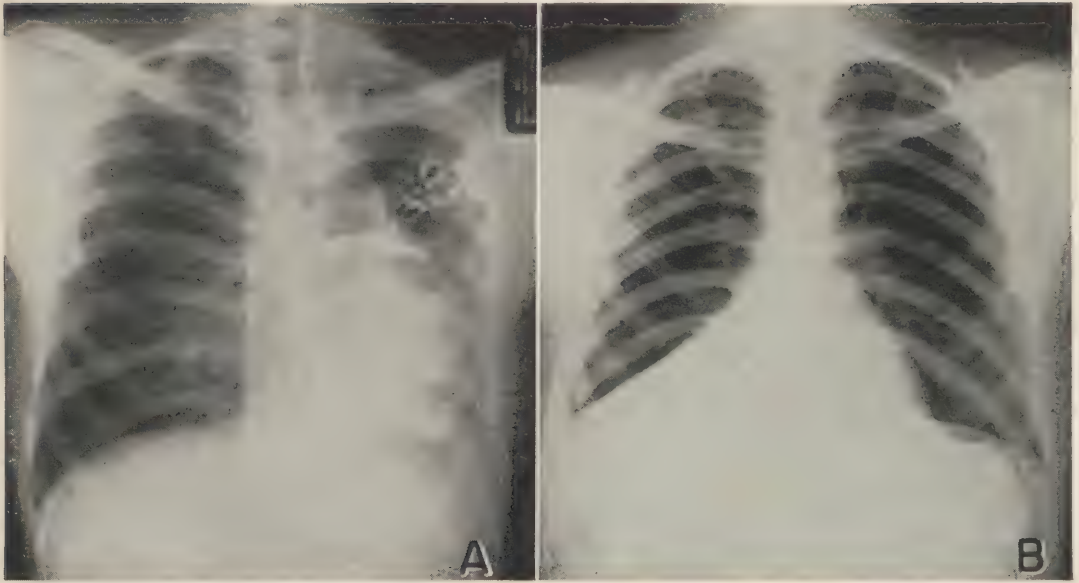


FIG. 1. *a.* Case 26. Blockage of the left lower lobe bronchus with atelectasis and bronchiectasis secondary to carcinoid type of bronchial adenoma. Neg. 84296. *b.* Case 37. Atelectasis of the right lower lobe due to obstruction by a mixed-tumor type of adenoma in the right main bronchus. Neg. 84171.

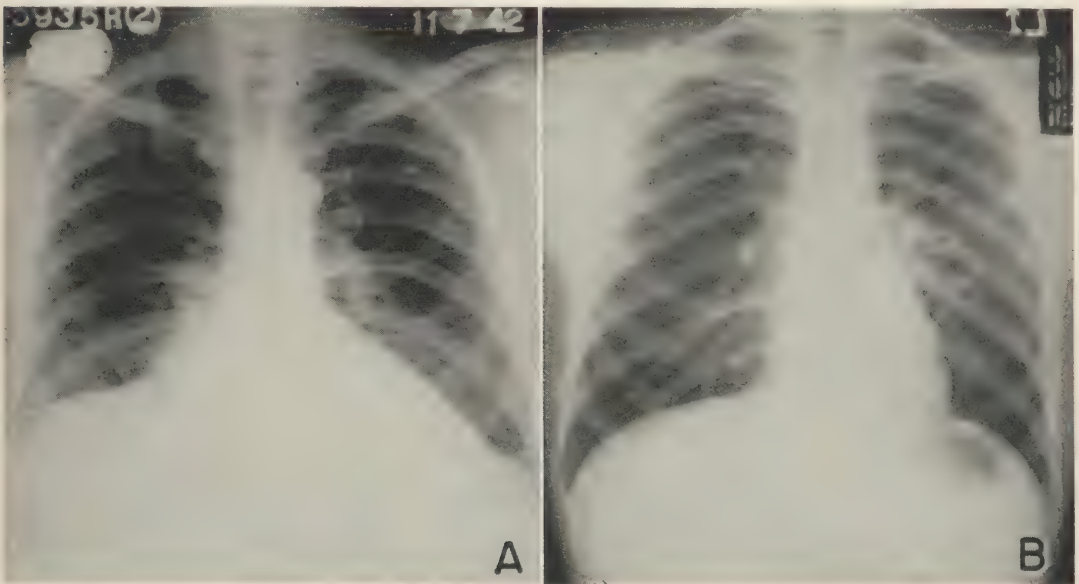


FIG. 2. *a.* Case 12. Slight medial atelectasis and inflammatory infiltrate in the right lower lobe. The adenoma was 3 cm. in diameter, of carcinoid type, and was located in the lower lobe (Fig. 5b) although that is not evident in the roentgenogram. Neg. 84775. *b.* Case 23. Inflammatory infiltrate and abscess in the left lower lobe secondary to carcinoid type of adenoma situated in the lower lobe bronchus. Neg. 83464.

tion showed the tumors usually covered by epithelium of either squamous or respiratory type or both with an underlying layer of connective tissue. (Figs. 7a and b.) Of the 23 cases in which sections included sufficient bron-

chial wall for interpretation, neoplastic cells had infiltrated peripherally in 15 (Fig. 14). In one case they were in the pulmonary alveoli (Figure 14c). Perivascular permeation of tumor cells was noted in at least 2 cases (Figs.

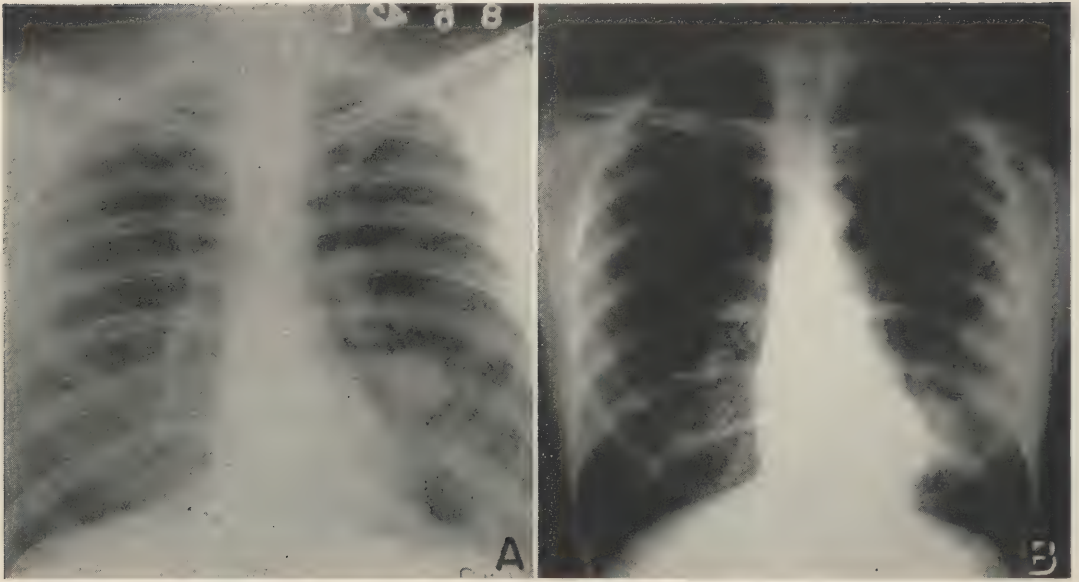


FIG. 3. *a.* Case 10. Mass (carcinoid type of adenoma) and inflammatory infiltration in the lower lobe of the left lung. Neg. 74472. *b.* Case 35. Mass in lower lobe of left lung (mixed-tumor type of adenoma). Neg. 92475.



FIG. 4. *a.* Case 34. Polypoid adenoma (carcinoid type) at the bifurcation of the right middle and lower lobe bronchi. Neg. 92476. *b.* Case 38. Polypoid adenoma (mixed-tumor type) in the left main bronchus. Photographs show actual size. Neg. 91530.

14d and e), and in another the cells were found in blood and lymphatic vessels (Fig. 15). There were two instances of metastasis to the regional lymph nodes (Figs. 16 and 17), and once tumor cells were found in the capsule of a peribronchial node (Fig. 14b).

Hepatic metastases were demonstrated in one case (Fig. 18).

Bone was present in the tumor in 8 cases (Fig. 11), usually near or contiguous with bronchial cartilages. In 3 cases, however, it seemed to have arisen in the connective tissue

of the tumor. In 2 cases there were calcium deposits in the stroma, and in one a part of the subepithelial fibrous layer was calcified (Fig. 7b). Where cartilage was found within a tumor it was mature, of hyaline type, and was so placed with respect to definite bronchial cartilages that its non-neoplastic nature could not be doubted. Bronchial glands were often separated by tumor, and occasionally nerves and smooth muscle bundles were isolated by it. Fat was in close association with tumor cells in 2 cases (Fig. 13c), but did not appear to be

inflammation was found in 18 of the lobectomy and pneumonectomy specimens. The changes were in the form of chronic bronchitis, bronchiectasis, interstitial pneumonitis and pleuritis. Suppuration was conspicuous in only a few cases.

DISCUSSION

The greater number of men in this series of bronchial adenomas must be related to the fact that the Army Institute of Pathology draws most of its material from the

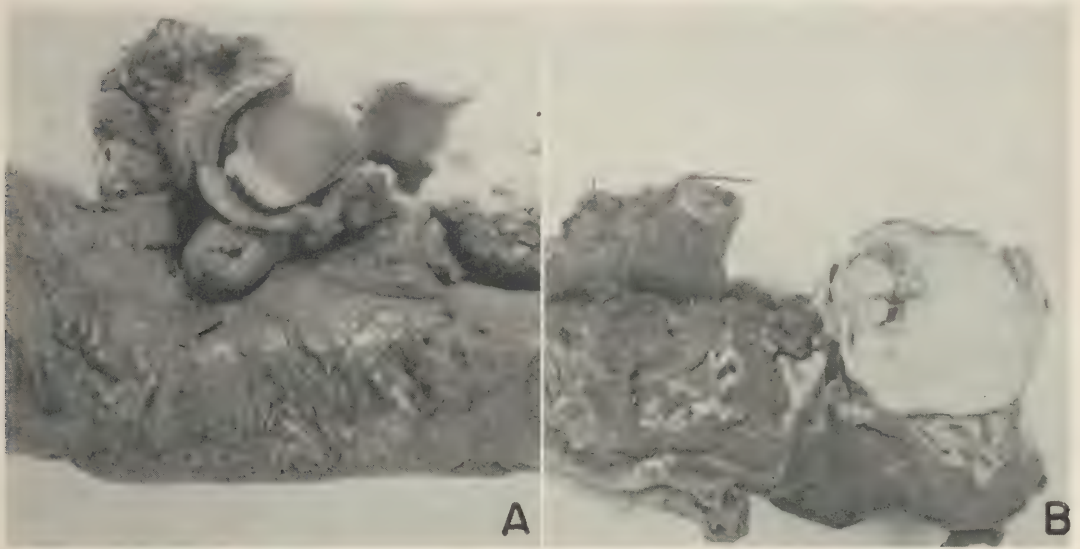


FIG. 5. *a.* Case 26. Pedunculated adenoma (carcinoid type) blocking the left main bronchus, although arising in the orifice of the upper lobe bronchus. Neg. 90523. *b.* Case 12. Well demarcated adenoma (carcinoid type) at hilus of the lower lobe of the right lung. Involved bronchus is not known. Photographs show actual size. Neg. 84270.

neoplastic. Vascularity was a prominent feature of several of the tumors, but was not a constant finding; necrosis was rare.

The descriptions of the tumor cells and their characteristic arrangements were included in the accounts of the representative cases and need not be repeated. Emphasis should be placed on the fact that mitoses were not seen except in one case (Case 35). Special stains revealed nothing distinctive in cell morphology except in the one case in which silver-positive granules were demonstrated by the Fontana stain (Fig. 10b). Fat was not found in the tumor cells.

Gross or microscopic evidence of chronic

medical service of the Army. Therefore, the figures relating to sex incidence should be disregarded in favor of those derived from series reported from the civilian population, which range from 54 per cent,³⁰ to 80 per cent in women,²⁴ the average from a number of reports being 62 per cent.¹⁸

Types: Although the clinical features of these neoplasms were remarkably uniform, the tumors could be readily separated into two histologic types on the basis of distinct differences in cell pattern and structure.

The larger group consisting of 34 cases has been called the carcinoid type of bronchial adenoma because the cells, their arrangement,

and the growth characteristics of the tumor were similar to, and in several instances identical with, appendiceal carcinoids. It is this type of tumor which is usually referred to as bronchial adenoma (Figs. 7, 8, 9, 10, 11).

The other type, represented by 5 cases (Figs. 12 and 13), has been classified as

it is retained because it suggests that the cells and cell patterns common to this type of bronchial adenoma resemble those of some of the mixed tumors.

Division of the bronchial adenomas into histologic types is not new. Hamperl¹¹ classified the tumors as bronchial carcinoids and cylind-



FIG. 6. *a.* Case 28. Sharply circumscribed bronchial adenoma (carcinoid type) in hilus of the upper lobe of the right lung. Neg. 84407. *b.* The same specimen at a different level. The tumor has filled the lumens of two bronchi adjacent to the main mass. Specimen is shown in its actual size. Neg. 84407.

bronchial adenoma of mixed-tumor type because of its close resemblance to some of the mixed tumors of salivary, lacrimal, and other glands about the mouth and orbit, as well as to some epithelial tumors in the jaws. However, in bronchial adenomas the stroma is not of the myxomatous, osteoid, or cartilaginous type usually associated with mixed tumors. To this extent the term is a misnomer, but

dromas. Laff and Neuburger²¹ recognized a carcinoid-like pattern and a cylindromatous one. The resemblance of this group of tumors as a whole to carcinoids has been noted by several observers.^{15,28,31,32} The term bronchial carcinoid has been rejected by most authors because silver-positive granules found in most appendiceal carcinoids could not be demonstrated in the cells of the bronchial tumors.

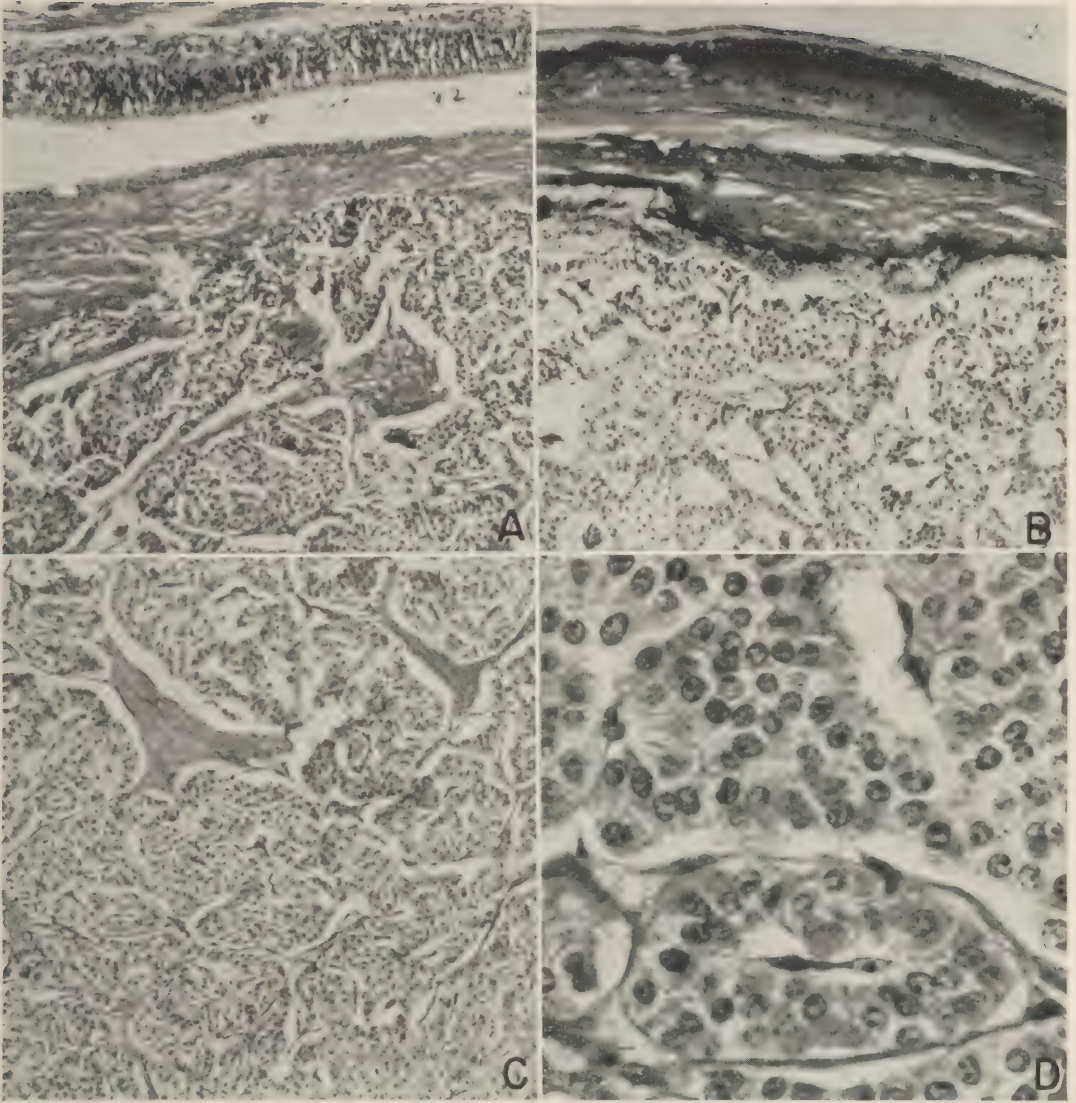


FIG. 7. Case 12. Carcinoid type of bronchial adenoma. *a*. Tumor separated from the bronchial lumen by connective tissue and thinned epithelium. Normal respiratory epithelium lies above the bronchial lumen. \times -130. Neg. 90987. *b*. Calcified connective tissue layer between the tumor and the thinned surface epithelium. \times -130. Neg. 90984. *c*. Typical carcinoid pattern. \times -130. Neg. 90985. *d*. Two pseudoglands with central spaces containing retracted connective tissue. \times -600. Neg. 90986. Refer to Figs. 2a, 5b and 11a for additional photographs in this case.

It will be recalled that such granules were found in the biopsy tissue from one tumor of this series (Fig. 10b).

The carcinoid type of bronchial adenoma also resembles certain other tumors. For example, a striking histologic likeness between it and the islet cell tumors of the pancreas was observed by Moore,³³ who studied some of the cases in this series, as well as by other investi-

gators.^{21,28} These observations are noteworthy because Boyd³⁴ referred to a similarity between pancreatic islet cell tumors and carcinoids of the appendix. Moersch, Tinney and McDonald²⁸ pointed out the close resemblance between bronchial adenomas and basal cell carcinomas of the skin and adenomas of the parathyroid gland.

Womack and Graham¹² regarded all bron-

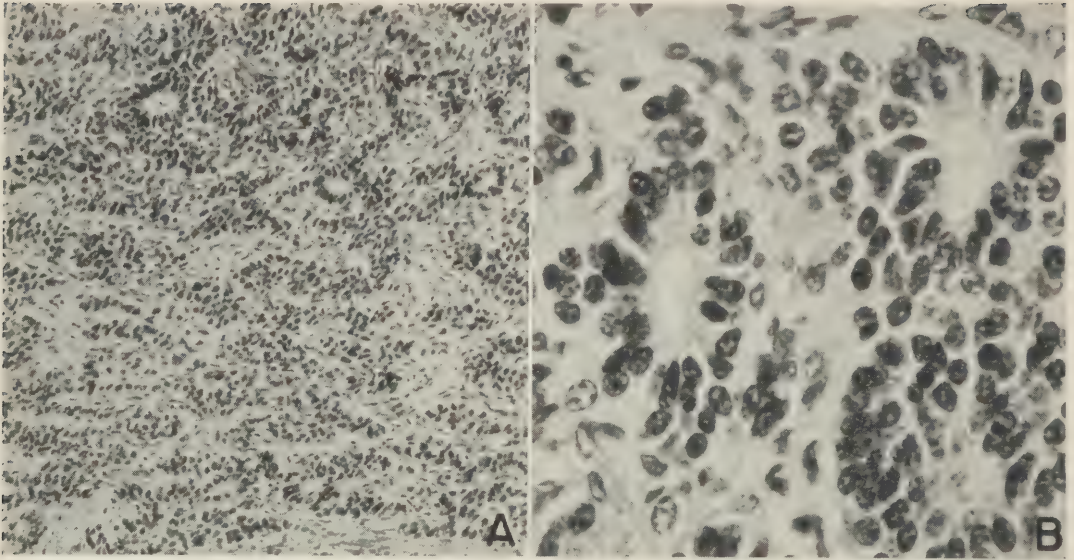


FIG. 8. Case 25. Carcinoid type of bronchial adenoma. *a.* Poorly defined cords and a few glands composed of tumor cells, the only case of this type in the present study showing distinct gland formation. \times -130. Neg. 91013. *b.* Glands composed of tumor cells. \times -600. Neg. 91015.

chial adenomas as mixed tumors without differentiation into types. They based their interpretation upon the presence of fat, cartilage, bone and smooth muscle in some of the tumors which they studied. Bone, noted rarely by most observers, was interpreted by Mallory¹⁵ as secondary to the tumor and not actually a part

of it. Moersch, Tinney and McDonald²⁸ believed that the bone resulted from ossification of bronchial cartilages. Brunn and Goldman¹⁷ were of the opinion that both bone and cartilage probably arose from dedifferentiation of adult tumor cells. Although bone was found in several of the carcinoid-type tumors in the

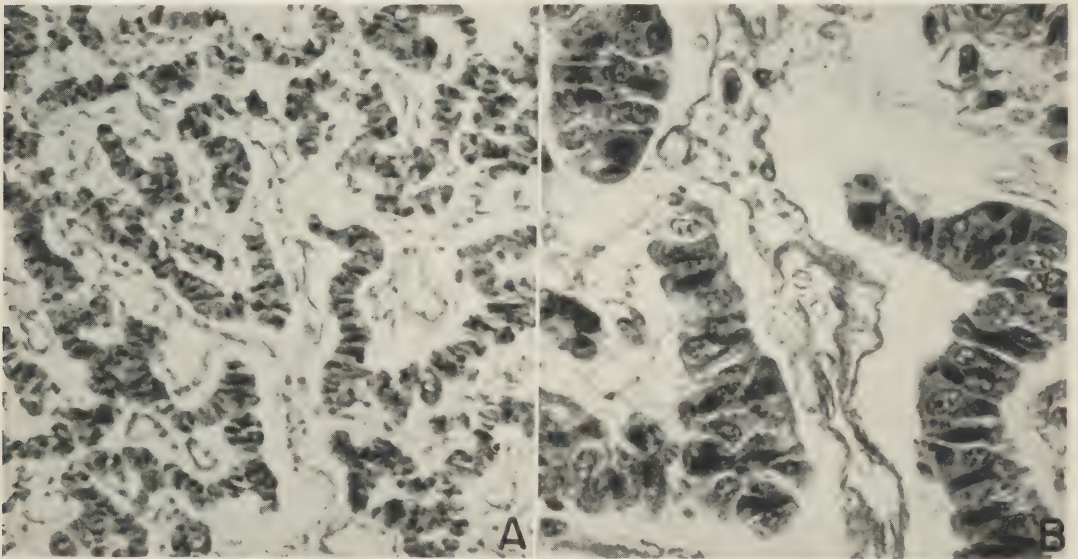


FIG. 9. Case 7. Carcinoid type of bronchial adenoma. *a.* Tumor arranged in distinct ribbons throughout, characteristic of certain carcinoids. Spaces are shrinkage artefacts. \times -200. Neg. 92332. *b.* Ribbons of elongated tumor cells with long axes directed transversely; delicate stroma contains blood capillaries. \times -600. Neg. 92331.

present study, it did not give the impression of being neoplastic; neither did fat, cartilage, smooth muscle, nerves, and blood vessels which appeared to have been incorporated in the tumors as a result of their expansile and infiltrative properties. Clerf and Bucher³⁰ apparently accepted bronchial adenomas as mixed tumors and described three types based on differences in the pattern and appearance of the cells; one of their types corresponded to

some of the adenomas were like carcinoids and others like cylindromas, he believed that they were essentially the same. McDonald, Moersch and Tinney²⁹ regarded the cylindroma as a form of bronchial tumor apart from the adenoma, and compared it with what they called cylindroma of salivary glands and of skin.

The close resemblance of the mixed-tumor type of bronchial adenoma to some of the mixed tumors of salivary glands and to basal

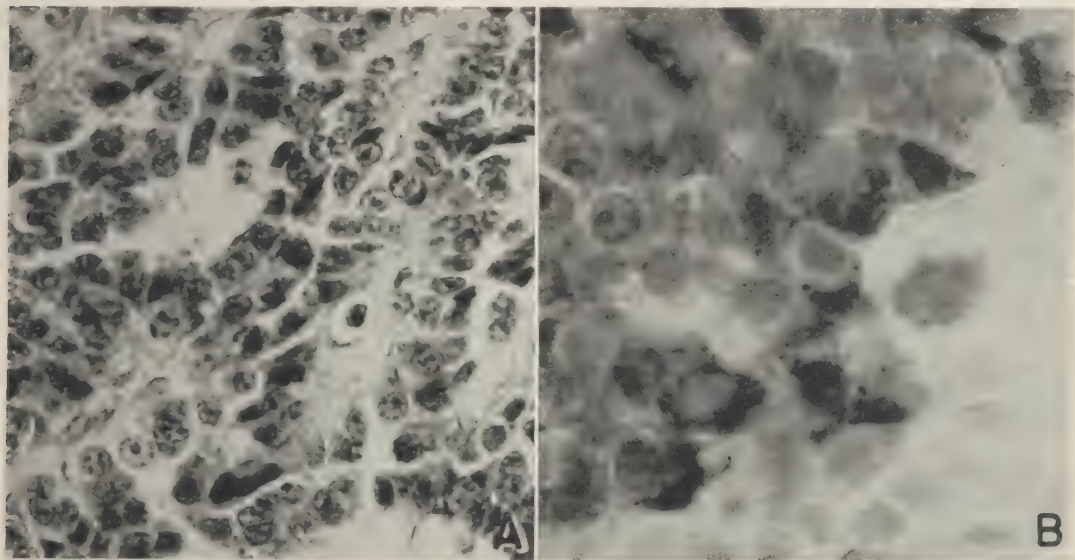


FIG. 10. Case 10. Carcinoid type of bronchial adenoma. *a.* Closely packed cords of tumor cells about a small irregular space, not gland-like, from lobectomy specimen. $\times 600$. Neg. 92312. *b.* Silver-positive granules (Fontana stain) within the cytoplasm of the tumor cells (from biopsy specimen). $\times 130$. Neg. 92311.

that which others have referred to as cylindroma. Foster-Carter¹⁸ concluded that bronchial adenomas were identical with benign salivary gland tumors.

The similarity of the mixed-tumor type of bronchial adenomas in the present series to epithelioma adenoides cysticum, to cylindroma, and in one case to the ordinary type of basal-cell carcinoma of the skin was striking. Similar observations have been made in other series. Geipel⁷ called the bronchial adenomas which he studied basal cell carcinomas, and Hamperl¹¹ used the term cylindroma for the mixed-tumor type. Stout²⁰ recognized a bronchial mixed tumor in addition to the typical adenoma. Although Anderson¹⁹ made the observation that

cell carcinomas of the skin is interesting, because Krompecher, cited by Ewing,³⁸ and Ewing himself noted the similarity between some of the mixed tumors of salivary glands and basal cell carcinomas of the skin, particularly epithelioma adenoides cysticum.

It is evident from the descriptions and illustrations appearing in the various papers that the 5 tumors classified in the present series as mixed-tumor type of bronchial adenoma are the same as bronchial tumors referred to by others as cylindromas or as simulating cylindromas. Which term is to be used, and whether the tumors are to be regarded as a type of bronchial adenoma or as an independent neoplasm is a matter for personal de-

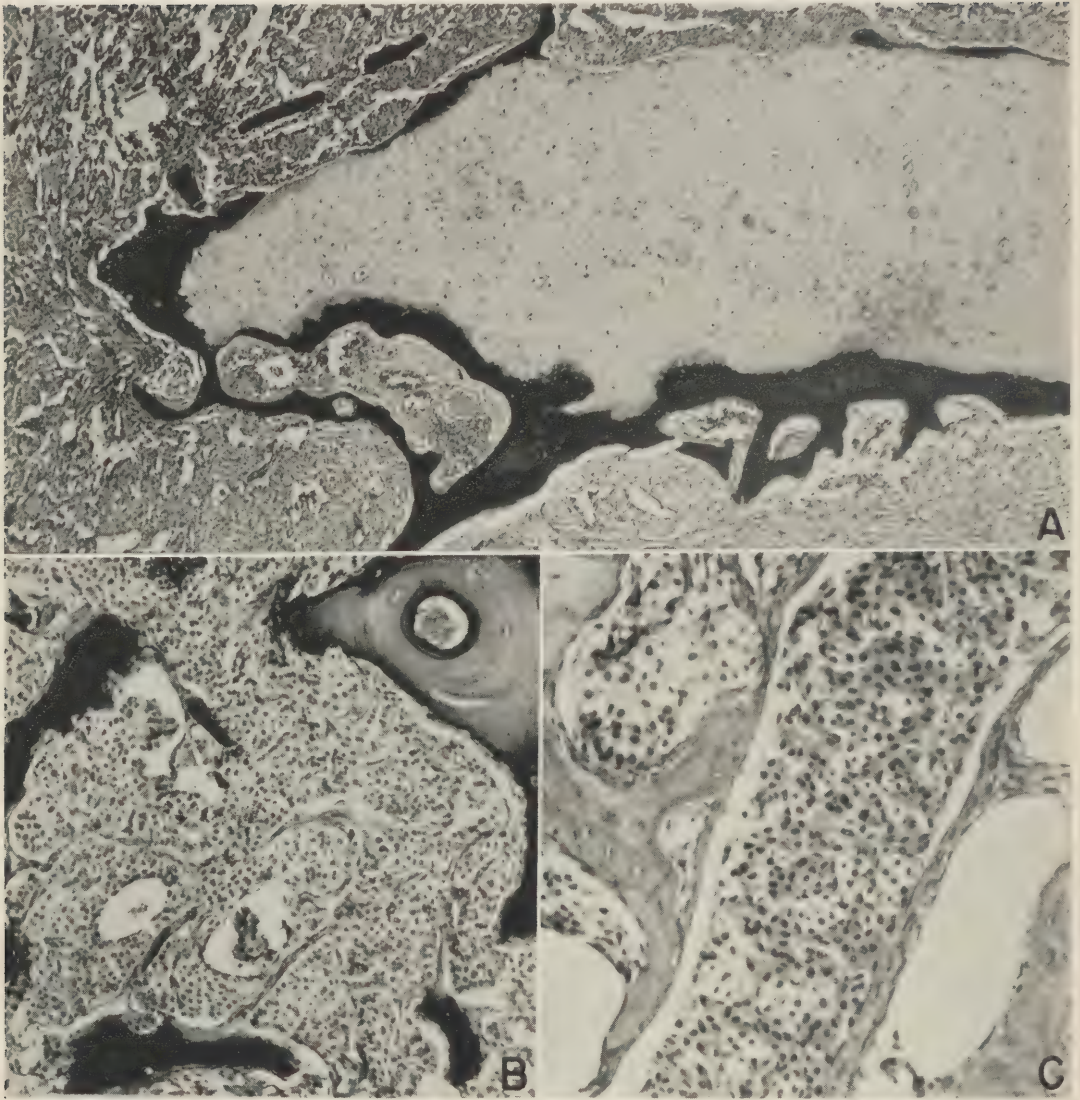


FIG. 11. Bone in carcinoid type of adenomas. *a.* Case 12. Ossification in the periphery of and about a bronchial cartilage. Note tumor in osseous spaces and between spicules near cartilage. $\times 50$. Neg. 90983. *b.* Case 16. Bone spicules in tumor. Note well developed portion of bone in upper corner on the right. $\times 130$. Neg. 91011. *c.* Case 9. Osseous stroma separating sheets of tumor cells. These cells are like those of cases showing a more distinct carcinoid pattern. $\times 200$. Neg. 92325.

termination. This tumor comprised 12.8 per cent of the adenomas of this series and 13.6 per cent of the combined bronchial adenomas and cylindromas as classified by McDonald, Moersch and Tinney.

The relationships of bronchial adenomas of both types, carcinoids, pancreatic islet cell tumors, different varieties of basal cell carcinoma of the skin, and certain tumors of the

salivary glands and other structures about the mouth and face remain to be explained.

Origin: The origin of bronchial adenomas although often discussed is still undetermined. If they are primarily epithelial tumors, as they are believed to be, they should arise from the bronchial surface, from the bronchial ducts, or from the mucous and serous glands. However, most writers agree that origin from the

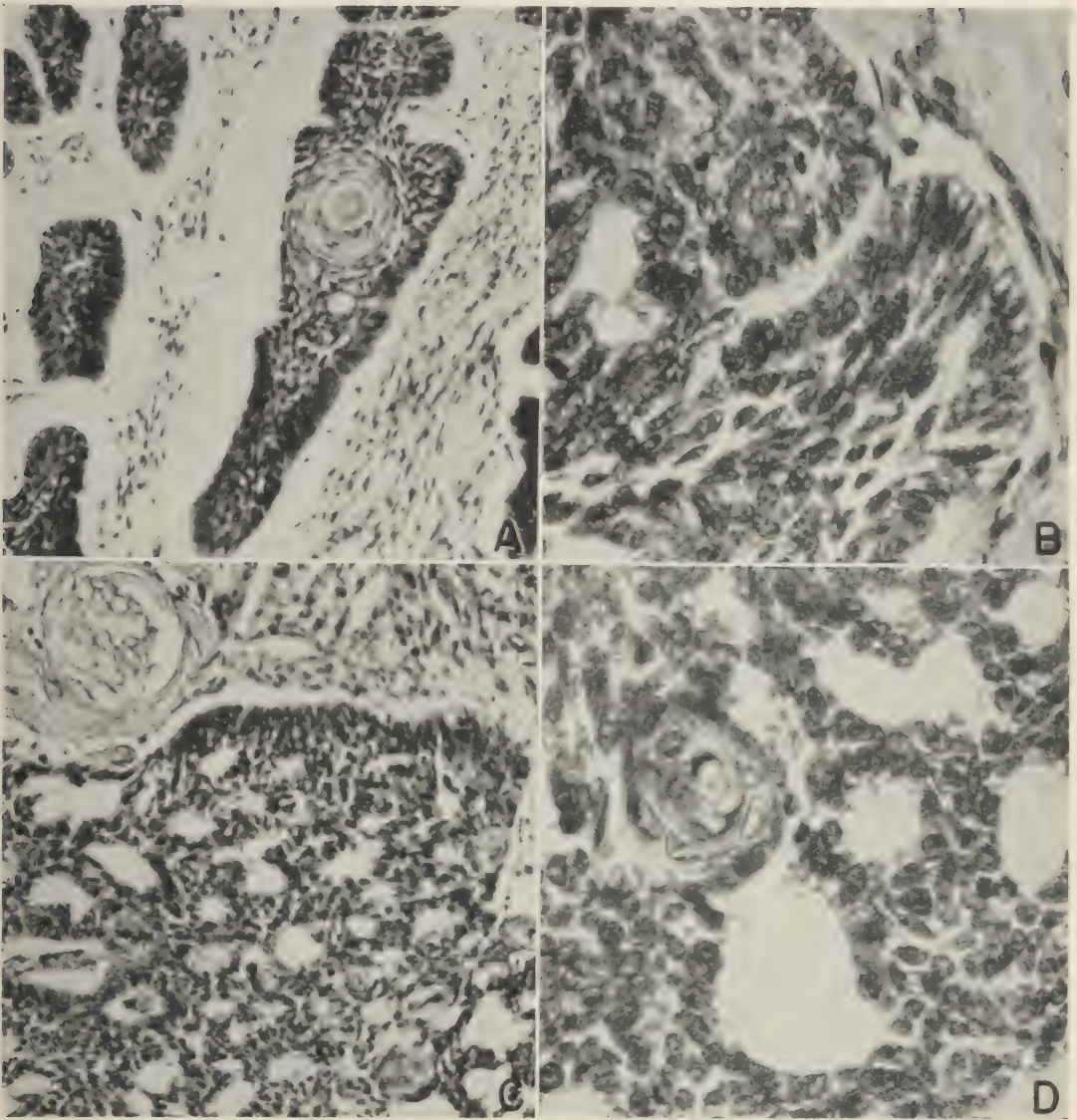


FIG. 12. Case 35. Mixed-tumor type of bronchial adenoma. *a.* Nests of tumor cells simulating basal cell carcinoma. Note whorl of squamous cells. $\times 200$. Neg. 92322. *b.* Higher magnification of area similar to *a.* $\times 600$. Neg. 92320. *c.* More solid portion of tumor, showing pattern of some salivary gland mixed tumors. Note close resemblance to epithelioma adenoides cysticum. $\times 200$. Neg. 92402. *d.* Area from portion similar to *c.* Contrast these cells and their arrangement, also those in *b*, with those of the carcinoid type of adenoma. $\times 600$. Neg. 93298.

surface epithelium is unlikely because the tumors are separated from it by a connective tissue layer. The most frequent suggestion is that they arise from the bronchial glands or ducts. Reisner,⁶ Kramer¹ and Wessler and Rabin² believed that they arose from bronchial ducts, Fried³⁶ and others^{9,18,37} that they originated in the bronchial glands. Brunn and

Goldman¹⁷ suggested that they might arise from both ducts and glands, and that the fact that the glands are normally of the mixed type might account for the variations in pattern encountered among the tumors. Stout²⁰ presented evidence in support of Hamperl¹¹ favoring a special cell, the oncocyte, as the probable source. The cell is found, according

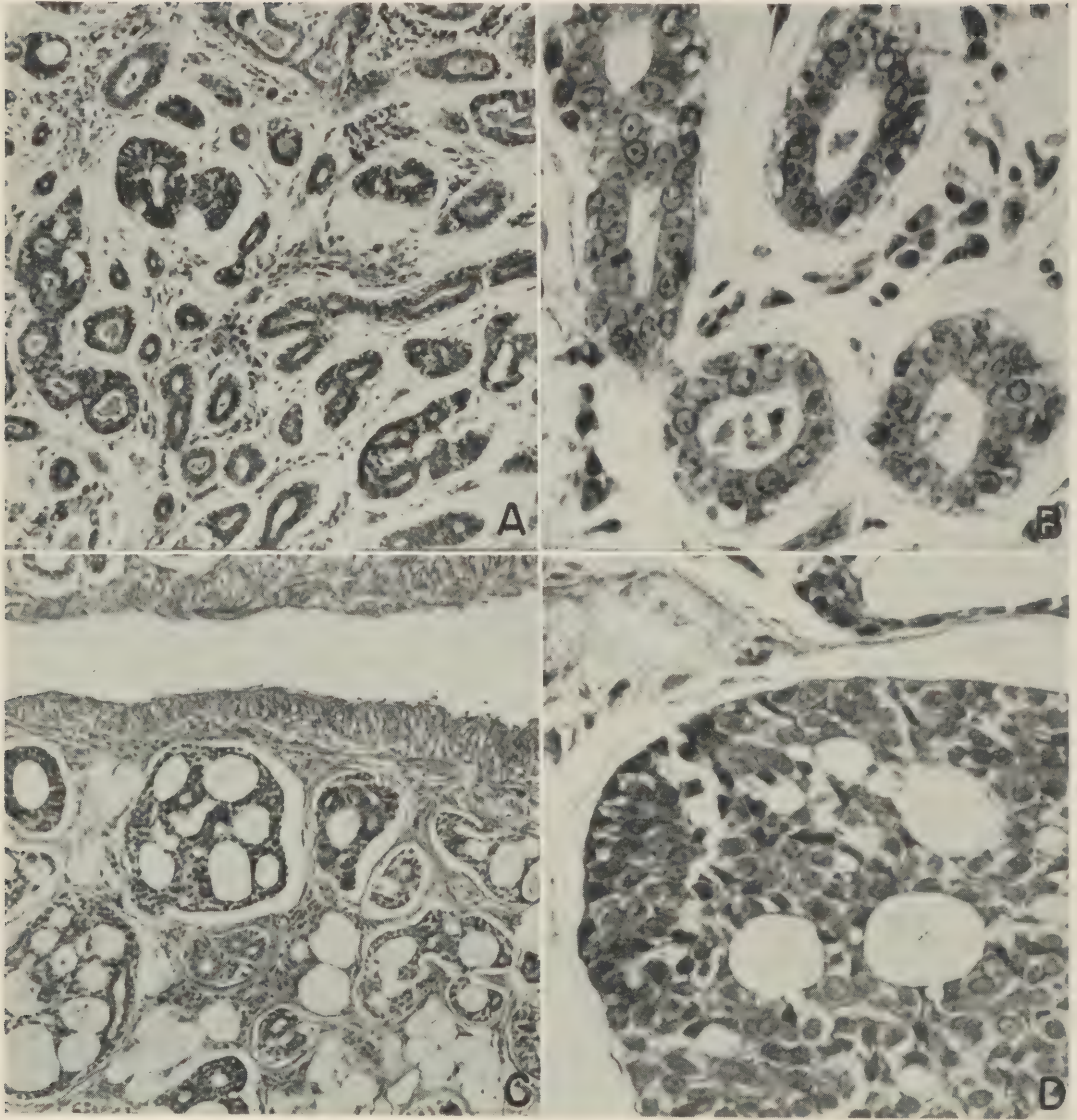


FIG. 13. Case 37. Mixed tumor type of bronchial adenoma. *a* and *b*. Tubular portion of tumor of adenomatoid pattern. Note homogeneous material in several lumens in *a*. \times -130. Neg. 91023, 91024. *c* and *d*. From another portion of the same tumor showing nests of cells adjacent to an artery and in adipose tissue in the outer part of the bronchial wall. Observe similarity to mixed tumor and to epithelioma adenoides cysticum. \times -130, \times -600, Neg. 91022, 93304.

to Stout, in the bronchial glands and ducts of adult human beings. Similar cells were demonstrated in some of the bronchial adenomas studied by Stout and in others examined by Hamperl.

Churchill³⁸ perceived a strong similarity between bronchial adenomas and the fetal lung and suggested that these tumors might be vestigial pulmonary lobes growing endobronchially.

Womack and Graham¹² likewise regarded their structure as like that of fetal lung and attributed their origin to undeveloped bronchial buds. In 2 or 3 biopsy specimens in this series there was some likeness to the fetal pattern, but it may well have been artefact, since it never was seen in sections of tumors removed by lobectomy or pneumonectomy. Harris and Schattenberg¹⁴ regarded bronchial

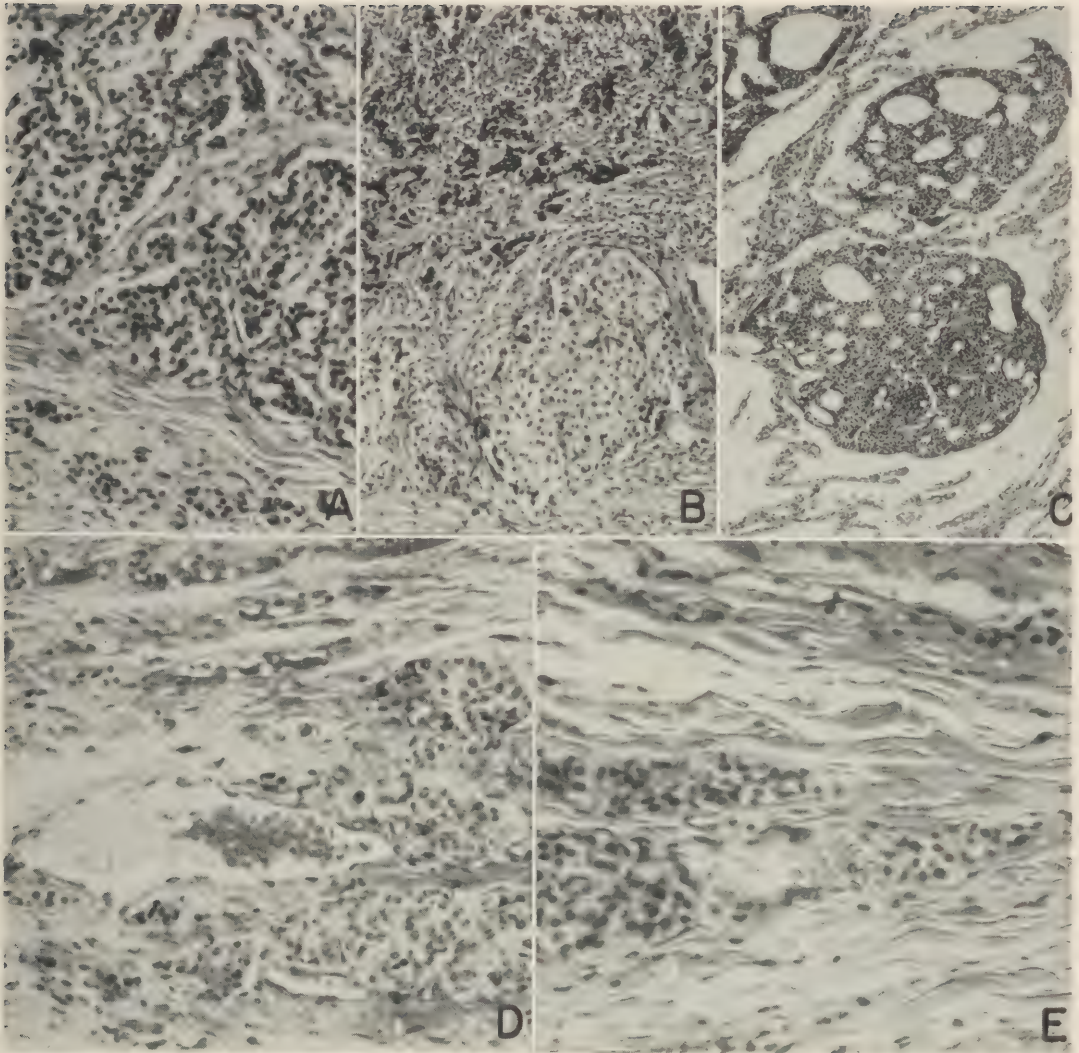


FIG. 14. Local tumor cell infiltration in bronchial adenomas. *a.* Case 34. Infiltration into connective tissue just outside margin of tumor (carcinoid type). $\times 200$. Neg. 92336. *b.* Case 12. Infiltration into capsule of peribronchial lymph node by direct or lymphatic extension (carcinoid type). $\times 130$. Neg. 91010. *c.* Case 35. Direct extension into pulmonary alveoli (mixed-tumor type). $\times 80$. Neg. 92321. *d.* Case 12. Extension adjacent to a small blood vessel (carcinoid type). $\times 235$. Neg. 92326. *e.* Case 34. Similar perivascular extension (carcinoid type). $\times 300$. Neg. 93303.

adenomas as probably developmental, and Harris³⁹ stated that they consisted in part of cells resembling lymphocytes. Because of these cells and the frequent vascularity of the tumors, Harris suggested that they might be referred to as adenomas of "secretory type" and "lymphoid or angiolymphoid type."

The origin of none of the tumors of this present series could be established on the basis of cell morphology or pattern. Cells compara-

ble to the oncocytes described by Hamperl and by Stout were not found. The carcinoid type of adenoma did not resemble any structure found in normal bronchi. Rarely, they contained a few gland-like structures, which, however did not simulate bronchial glands. Only by their position and apparent origin within the bronchial wall could one speculate that they might have begun in bronchial glands or ducts.

The origin of the mixed-tumor type would

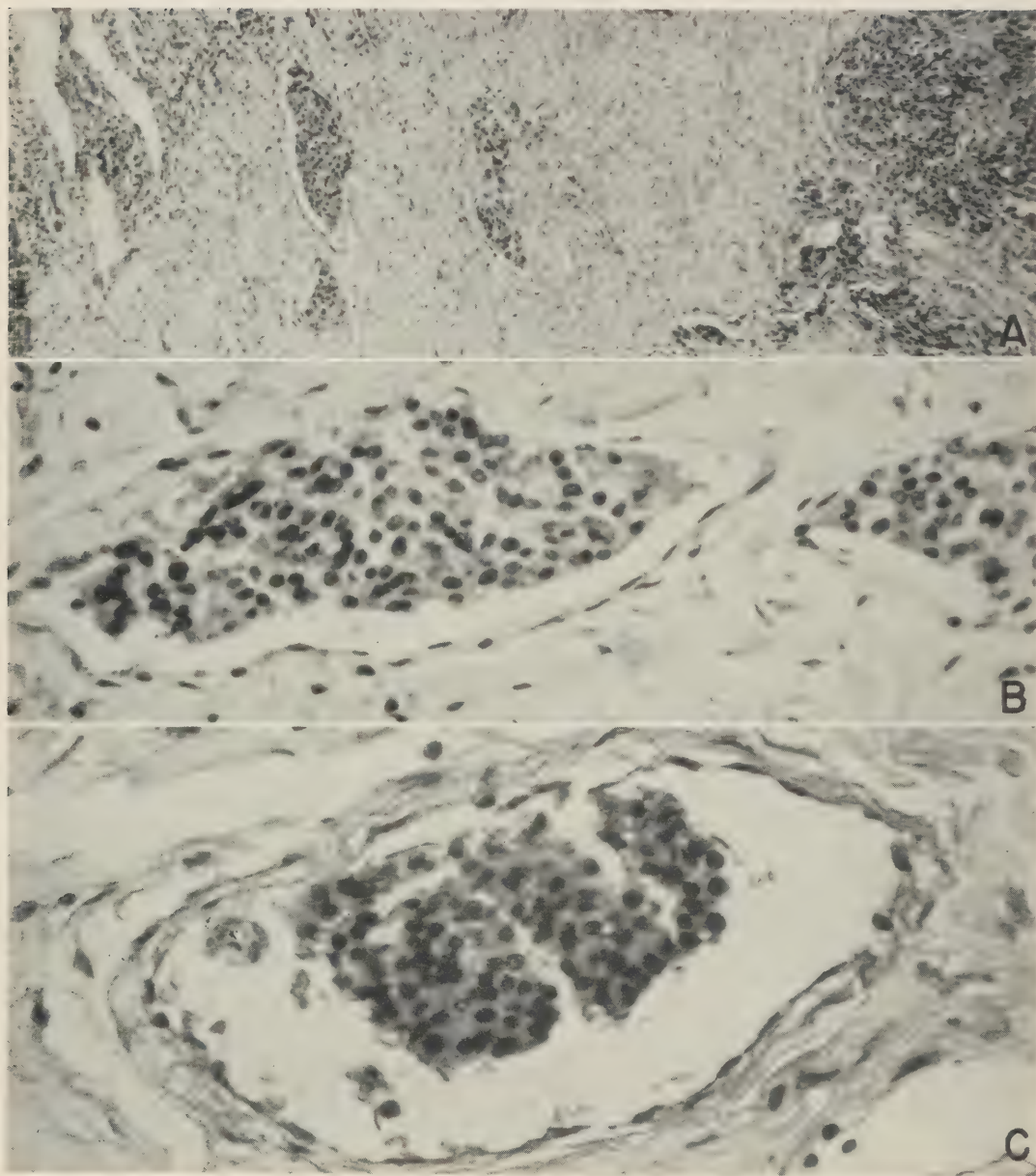


FIG. 15. Case 23. Vascular invasion by bronchial adenoma (carcinoid type). *a.* Tumor cells in blood or lymphatic vessels; tumor proper is at right, alveolar spaces at left. \times -130. Neg. 90989. *b.* Tumor cells in a lymphatic channel. \times -435. Neg. 90988. *c.* Tumor cells in a blood vessel. \times -600. Neg. 92327.

seem to be related to bronchial ducts or glands, though the material noted within spaces retained no specific stain to indicate that it was of gland-cell origin. In case 37 there was a resemblance between some of the neoplastic tubular structures and the normal ducts, but this does not prove that the ducts were the

source. Stout²⁰ attributes the origin of what he calls mixed tumor of the bronchus to the bronchial glands.

Malignant Potentialities: The status of bronchial adenomas with regard to malignancy is a most important problem. Therapy has not been uniform because of lack of agreement

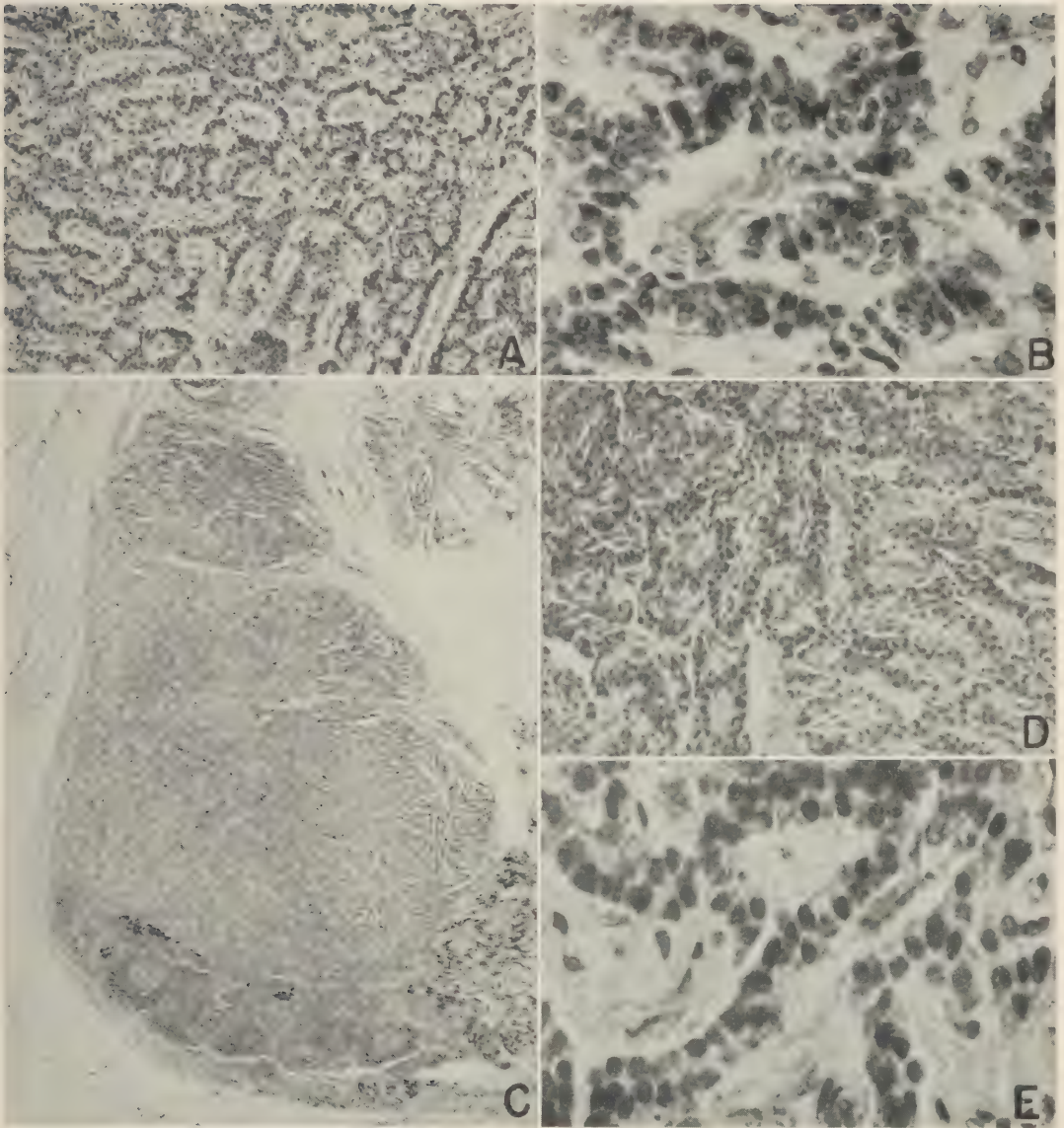


FIG. 16. Case 5. Metastasis of bronchial adenoma (carcinoid type). *a* and *b*. Pattern and cellular constituents of the primary bronchial tumor. \times -130, \times -600. Neg. 90976, 93294. *c*. Metastatic tumor tissue displacing and replacing lymphoid tissue and lying within capsule of the node. \times -25. Neg. 92304. *d* and *e*. Portions of metastasis as in *c*, showing pattern and cell type. \times -200, \times -600. Neg. 93297, 93296. (Note the remarkable similarity in the pattern and cells of the metastasis and those of the primary tumor.)

regarding their potentialities. Foster-Carter¹⁸ stated that metastasis was unknown but that local infiltration might occur. Clerf and Bucher³⁰ concluded that they were probably benign and non-metastasizing. Only one of the 35 cases which they studied presented evidence of malignancy, and this change did not appear until 5 years after discovery of the

original adenoma. Jackson, Konzelmann and Norris²⁴ stated that the adenomas do not metastasize and expressed doubt that they ever become malignant.

Wessler and Rabin² presented 2 cases as evidence that bronchial adenomas may become malignant. More recently there have been several unequivocal reports of extension beyond

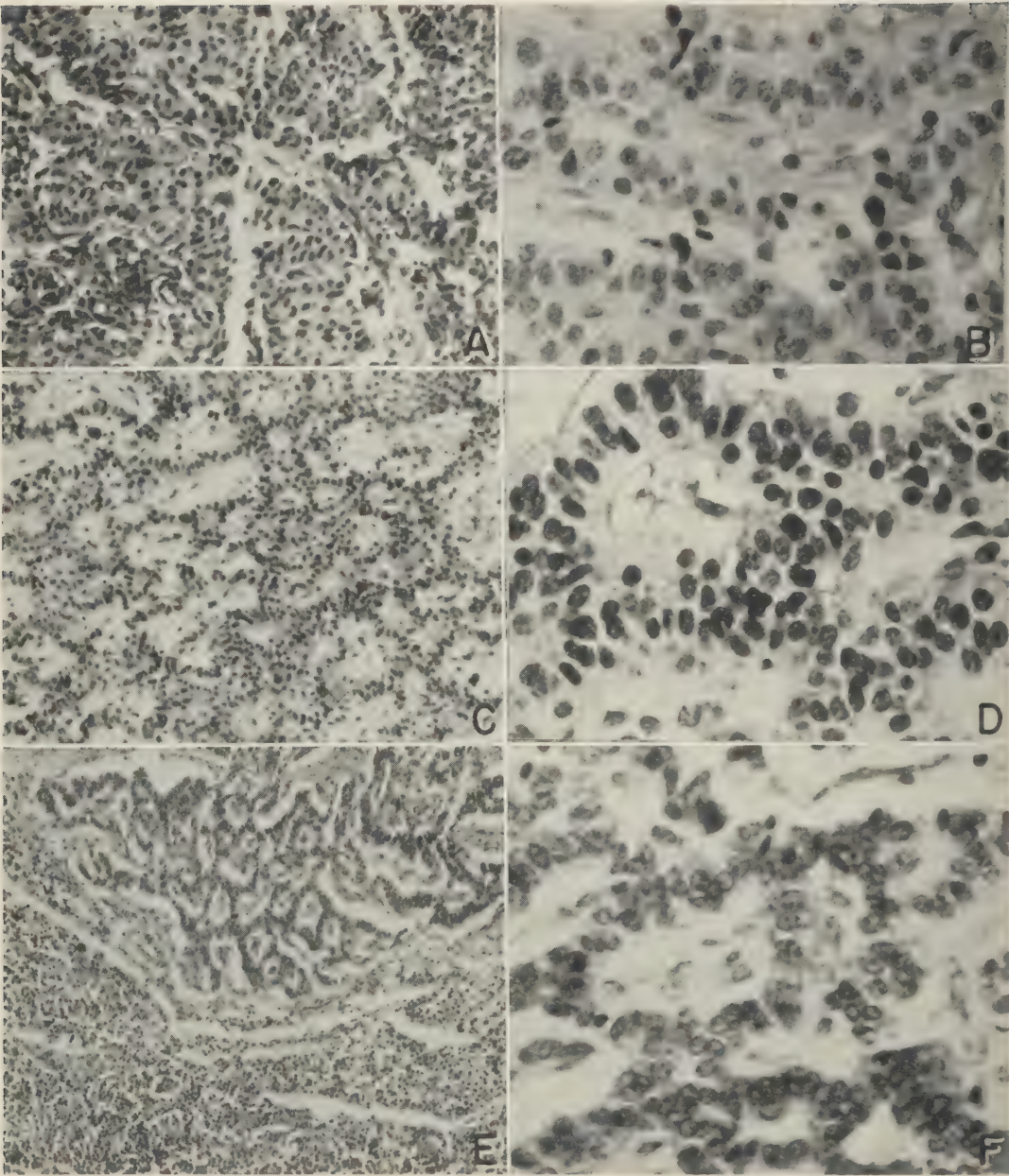


FIG. 17. Case 15. Bronchial adenoma (carcinoid type) with metastasis to lymph node. *a* and *b*. From bronchial biopsy specimen removed in 1937. \times -200, \times -600. Neg. 93292, 91006. *c* and *d*. From bronchial biopsy specimen removed in 1941. \times -200, \times -600. Neg. 92318, 93293. *e* and *f*. Interlacing cords of metastatic tumor cells in lymph node. (Autopsy-1943.) \times -130, \times -600. Note similarity of pattern and cells to bronchoscopic specimen of 1941 and to the cells of the 1937 specimen. Neg. 91007, 92329.

the borders of the original tumors. Castleman⁴⁰ described a case with metastasis to a regional lymph node. Adams, Steiner and Bloch¹³ presented 5 cases as malignant adenomas, because there was infiltration of the bronchial wall in

all, invasion of local lymphatics in 1, metastasis to the peribronchial lymph nodes in 2, and distant metastases in 2: one in the liver, the other in a vertebral body. The authors did not make any distinction as to pattern types.

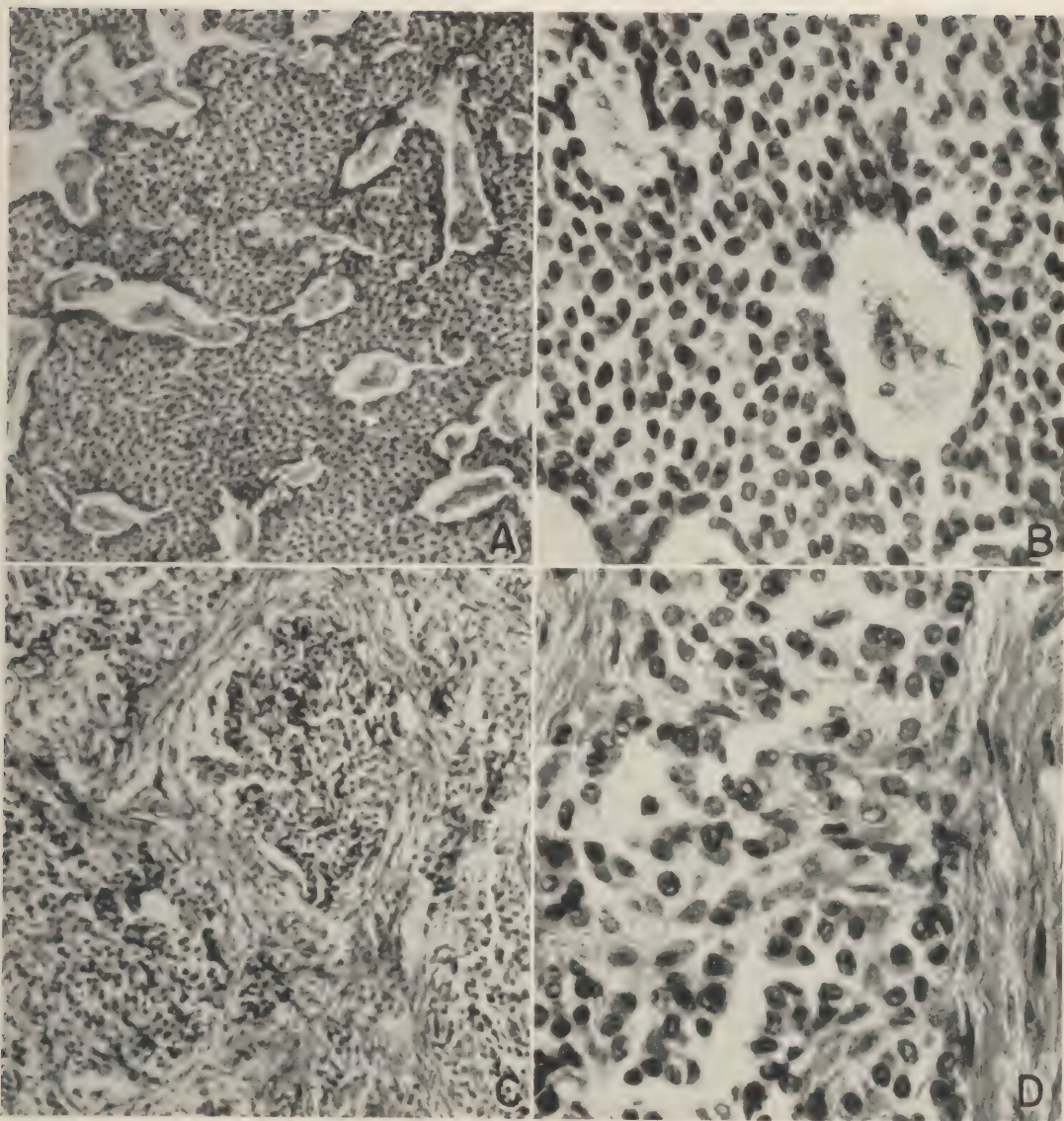


FIG. 18. Case 31. Metastasis of a bronchial adenoma to liver. *a* and *b*. Typical benign-appearing carcinoid type of pattern and cells from the primary bronchial tumor. $\times 200$, $\times 600$. Neg. 93293, 93291. *c* and *d*. Hepatic metastasis; pattern less distinct than in primary tumor, though cells are similar and carcinoid-like. $\times 200$, $\times 600$. Neg. 93288, 93289.

In Anderson's case¹⁹ with metastasis to the liver, the tumor in both the bronchus and the liver simulated cylindroma. Laff and Neubuerger²¹ reported an adenoma with cylindromatous features, which had metastasized extensively to the opposite lung. Moersch, Tinney and McDonald²⁸ described invasion of the bronchial wall in 13 of 15 of their cases, and found tumor tissue in a regional lymph node in 2. Extension into lymphatic and

blood vessels with distant metastasis has been described by Lentino.⁴¹

In the present study there were numerous examples of local infiltration of tumor cells. Lymph node metastasis was found in 2 cases, extension into a lymph node capsule in 1 case, vascular involvement in 1, and distant metastases (liver) in 1 case. The author has recently studied sections from an autopsy performed at the University of Illinois College

of Medicine showing a bronchial tumor of long standing which had metastasized to a kidney. The metastasis reproduced the cell type and pattern of the primary lesion accurately and was like the mixed-tumor type of bronchial adenoma described in this series. In none of these tumors with metastasis or local infiltration has there been any essential difference between the pattern and structure of the cells constituting the primary tumor and of those which have infiltrated or metastasized. The tumor cells have shown little or no anaplasia and even in metastases have appeared benign morphologically.

Laff and Neuburger²¹ have raised a question as to whether the bronchial adenoma of mixed-tumor type (referred to by them as the cylindromatous form) may not be more likely to metastasize. McDonald, Moersch and Tinney²⁹ have the impression that the tumors which they call bronchial cylindromas are more aggressive than the usual adenoma. In the cases of Clerf and Bucher³⁰ the clinical behavior of this type was considered to be the same as that of the other adenomas. The present series of cases does not help particularly in answering this question because tumors of both types infiltrated locally; three of the carcinoid type metastasized; one of the mixed-tumor type invaded alveoli; and another showed evidence of recurrence after lobectomy.

In the light of available information it is necessary to state that some bronchial adenomas become malignant. The most convincing evidence is that in doing so they retain their original pattern, and apparently continue their usual slow rate of growth, as is the rule with metastasizing carcinoids of the appendix, mixed tumors of the salivary glands, and basal cell carcinomas of the skin. Rarely, if ever, has death occurred because a previously recognized typical bronchial adenoma became malignant through accelerated rate of growth and capacity to metastasize widely as do the usual bronchogenic carcinomas. That they may completely lose their original features and follow the course of the usual bronchogenic carcinomas, as Graham and Womack²⁵ believe the

majority of them do, is difficult to prove or disprove, but remains a possibility. One bronchogenic carcinoma studied at the Army Institute of Pathology suggested such transition, but the material available did not permit examination adequate for conclusions.

Diagnosis: The diagnosis of the bronchial adenomas must depend finally upon tissue study, although the age at which they occur, the higher incidence in women, hemoptysis, cough, expectoration, recurrent acute pulmonary infection, and the roentgenologic features often give definite leads. The ability of bronchologists to identify these tumors in situ has contributed to their recognition. One must keep in mind that they have often been diagnosed as bronchogenic carcinomas, from which they should be distinguished even though some of them are malignant in the strict sense of the term. This differentiation is difficult at times because the cells of the adenomas may be elongated and their nuclei spindle-shaped and deeply stained, due to the distortion encountered in some biopsy specimens. This often gives the impression of extensive infiltration and anaplasia. In the past, patients with bronchial adenomas have been treated for months or even years for presumed tuberculosis. Bronchiectasis, atelectasis, and empyema have sometimes existed for long periods under the observation of a physician, the true cause of illness being overlooked. Bronchoscopic investigation is essential in the presence of any unexplained chronic pulmonary symptom or sign.

Treatment: The methods of therapy for bronchial adenomas may be found by referring to the papers of recent years. The trend seems to be away from bronchoscopic removal, X-ray, or local radium ray therapy, toward extirpation by lobectomy and pneumonectomy. Several factors are involved in this trend: the diminishing mortality rate from the more extensive thoracic operations; the size of the tumor and its peripheral cellular infiltration which may prevent endobronchial eradication; possible metastasis, and finally, associated bronchiectasis which of itself is justification for resection of a lobe or a lung.

The impression gained from the cases pre-

sented is that all bronchial adenomas should be removed by lobectomy or pneumonectomy as soon after discovery as is feasible, notwithstanding their apparently restricted malignant potentialities. A possible exception is the occasional small, pedunculated tumor without evidence of extrabronchial extension or bronchiectasis. Even so, there remains the possibility of recurrence and chronic pulmonary infection with tenacious adhesion of the lung to the chest wall, which may make subsequent lobectomy or pneumonectomy both difficult and dangerous.

Lobectomy is considered preferable to pneumonectomy if the remainder of the affected lung appears healthy and the tumor is so located that there is a reasonable chance of its extirpation. The procedure is less hazardous, and the patient is left a larger amount of functioning pulmonary tissue. Pneumonectomy is advocated if the tumor arises in one of the main (stem) bronchi or if it is so large that it has obstructed bronchi to all lobes with consequent chronic infection and loss of function of the entire lung. Evaluation of transthoracic bronchotomy for the removal of some of the smaller tumors must await further trial.

SUMMARY

1. In 38 patients with a bronchial adenoma the predominant symptoms and signs were cough, hemoptysis, recurrent acute respiratory infection, and expectoration. Roentgenographic features were those of atelectasis, bronchiectasis, pulmonary inflammation, bronchial blockage, and presence of a mass. All of these signs and symptoms were not present in the same patient. The tumor was found incidentally at autopsy in one additional case.

2. The tumors were located at or near the pulmonary hilus, were usually polypoid, and in several cases attained rather large size.

3. They assumed two distinct patterns, one which simulated that of appendiceal carcinoid and the other that of some of the mixed tumors of salivary glands and other structures of the mouth and face. They have been designated carcinoid type and mixed-tumor type of bronchial adenoma respectively.

4. The origin of neither of the types was determined, though their intramural location in the bronchus suggested bronchial glands or ducts as sources.

5. Several of the tumors exhibited features of malignancy. Some had infiltrated locally; one had filled several adjacent pulmonary alveoli; one had extended into a lymph node capsule; two had metastasized to a hilus lymph node; one had invaded small vessels, and one had metastasized to the liver.

6. This study indicates that lobectomy or pneumonectomy, according to the location of the tumor, is the preferred treatment because many of the tumors are of such size or have infiltrated so that they cannot be entirely removed through the bronchoscope; because of the malignant potentialities of some of the tumors; and because of the frequent coexistence of bronchiectasis and chronic pneumonitis.

The writer expresses his sincere appreciation to the clinicians and pathologists both in civilian and military service who submitted the cases presented and who secured follow-up information wherever possible. He is also grateful for the consultation photography and other help supplied by the professional and technical staff of the Army Institute of Pathology.

REFERENCES

- ¹Kramer, R.: Adenoma of bronchus, *Ann. Otol., Rhin. & Laryng.* 39:689-695, 1930.
- ²Wessler, H., and Rabin, C. B.: Benign tumors of the bronchus, *Am. J. M. Sc.* 183:164-180, 1932.
- ³Overholt, R. H.: Pneumonectomy for malignant and suppurative disease of the lung, *J. Thoracic Surg.* 9:17-61, 1939-40.
- ⁴Schwartz, L.: Adenoma of the trachea and bronchus, *Arch. Otolaryng.* 39:231-242, 1944.
- ⁵Tyson, M. D., and Milliken, N. T.: Total pneumonectomy for benign bronchial adenoma, *Am. J. Surg.* 67:111-118, 1945.
- ⁶Reisner, D.: Intrabronchial polypoid adenoma, *Arch. Surg.* 16:1201-1213, 1928.
- ⁷Geipel, P.: Zur Kenntnis der gutartigen Bronchialtumoren, *Frankfurt. Ztschr. f. Path.* 42:516-544, 1931.
- ⁸Rosenblum, P., and Klein, R. I.: Adenomatous polyp of the right main bronchus producing atelectasis, *J. Pediat.* 7:791-796, 1935.
- ⁹Clerf, L. H., and Crawford, B. L.: Benign glandular tumors of the bronchus, *Tr. Coll. Phys., Philadelphia*, 4th Series, 4:6-8, 1936.

- ²⁰ Zamora, A. M., and Schuster, N.: Vascular adenoma of the bronchus, *J. Laryng. & Otol.*, 52: 337-343, 1937.
- ²¹ Hamperl, H.: Über gutartige Bronchialtumoren (Cylindrome und Carcinome), *Virchow's Arch. f. path. Anat.* 300:46-88, 1937.
- ²² Womack, N. A., and Graham, E. A.: Mixed tumors of the lung, so-called bronchial or pulmonary adenomas, *Arch. Path.* 26:165-206, 1938.
- ²³ Adams, W. E., Steiner, P. E., and Block, R. G.: Malignant adenoma of the lung, carcinoma-like tumors with long clinical course, *Surgery* 11:503-526, 1942.
- ²⁴ Harris, W. H., and Schattenberg, H. J.: Anlagen and rest tumors of the lung inclusive of "mixed tumors" (Womack and Graham). *Am. J. Path.* 18: 955-967, 1942.
- ²⁵ Mallory, T. B.: Case records of the Massachusetts General Hospital; Case 27511, *New England J. Med.* 225:983-986, 1941.
- ²⁶ Goldman, A., and Stephens, H. B.: Polypoid bronchial tumors with special reference to bronchial adenomas, *J. Thoracic Surg.* 10:327-353, 1941.
- ²⁷ Brunn, H., and Goldman, A.: Bronchial adenoma, *Am. J. Surg.* 54:179-192, 1941.
- ²⁸ Foster-Carter, A. F.: Bronchial adenoma, *Quart. J. Med.* 10:139-174, 1941.
- ²⁹ Anderson, W. M.: Bronchial adenoma with metastasis to the liver, *J. Thoracic Surg.* 12:351-360, 1942-43.
- ³⁰ Stout, A. P.: Cellular origin of bronchial adenoma, *Arch. Path.* 35:803-807, 1943.
- ³¹ Laff, H. I., and Neuburger, K. T.: Bronchial adenoma with metastasis, *Arch. Otolaryng.* 40:487-493, 1944.
- ³² Riordan, D. C., and Richards, V.: Bronchial adenoma, report of an unusual case: review of the literature, *Stanford Med. Bull.* 2:63-71, 1944.
- ³³ Nager, R.: Über das sogenannte Bronchialadenoma, *Praxis* 33:84, 1944.
- ³⁴ Jackson, C. L., Konzelmann, F. W., and Norris, C. M.: Bronchial adenoma, *J. Thoracic Surg.* 14: 98-105, 1945.
- ³⁵ Graham, E. A., and Womack, N. A.: The problem of the so-called bronchial adenoma, *J. Thoracic Surg.* 14:106-119, 1945.
- ³⁶ Chamberlain, J. M., and Gordon, J.: Bronchial adenoma treated by pulmonary resection, *J. Thoracic Surg.* 14:144-159, 1945.
- ³⁷ Harris, H. E.: Adenoma of the bronchus, *Cleveland Clin. Quart.* 12:73-80, 1945.
- ³⁸ Moersch, H. J., Tinney, W. S., and McDonald, J. R.: Adenoma of the bronchus, *Surg. Gynec. & Obst.* 81:551-558, 1945.
- ³⁹ McDonald, J. R., Moersch, H. J., and Tinney, W. S.: Cylindroma of the bronchus, *J. Thoracic Surg.* 14:445-453, 1945.
- ⁴⁰ Clerf, L. H., and Bucher, C. J.: Adenoma (mixed tumor) of bronchus: a study of 35 cases, *Ann. Otol., Rhin. & Laryng.* 51:836-850, 1942.
- ⁴¹ Kernan, J. D.: Treatment of a series of cases of so-called carcinoid tumors of the bronchi by diathermy, report of 10 cases, *Ann. Otol. Rhin. & Laryng.* 44:1167-1191, 1935.
- ⁴² Jackson, C. L., and Konzelmann, F. W.: Bronchoscopic aspects of bronchial tumors with special reference to so-called bronchial adenoma, *J. Thoracic Surg.* 6:312-329, 1936-37.
- ⁴³ Moore, R. A.: Personal communication.
- ⁴⁴ Boyd, W.: *Surgical Pathology*, ed. 4, Philadelphia, W. B. Saunders Co., p. 341, 1938.
- ⁴⁵ Ewing, J.: *Neoplastic Diseases*, ed. 4, Philadelphia, W. B. Saunders Co., pp. 790-791, 1940.
- ⁴⁶ Fried, B. M.: Adenoma of bronchial mucous glands, *Arch. Otolaryng.* 20:375-381, 1934.
- ⁴⁷ Brock, R. C.: Pulmonary new-growths, *Lancet* 2:1041-1044, 1938.
- ⁴⁸ Churchill, E. D.: Discussion of symposium on surgery of the lungs and mediastinum, *J. Thoracic Surg.* 6:335, 1936-37.
- ⁴⁹ Harris, W. H.: Histologic analogy of bronchial adenoma to late prenatal and early postnatal structures, *Arch. Path.* 35:85-92, 1943.
- ⁵⁰ Castleman, B.: Case records of the Massachusetts General Hospital; Case 26171, *New England J. Med.* 222:721-724, 1940.
- ⁵¹ Lentino, A. S.: Tumores mixtos del pulmon (adenomas bronquiales), *Bal. Inst.-Clin. Quir. Buenos Aires* 21:113-122, 1945.

THE PATHOLOGY OF ACUTE FALCIPARUM MALARIA*

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(With thirty-two illustrations)

FALCIPARUM malaria obviously will not reach the epidemic proportions in the United States that were anticipated during World War II chiefly because the suppressive atabrine therapy used by the Armed Forces in all endemic areas has proved of greater curative value against *Plasmodium falciparum* than against other malarial parasites. However, this form of the disease is still sufficiently common in this country as to be of concern; indeed, as the reports by Helsen¹ of epidemics among drug addicts indicate, falciparum malaria was, on occasion, a distinct problem even before the war. Although the pathologic anatomy of malaria has been previously studied in a most adequate fashion, it appears likely that, in the light of current investigation of the clinical, physiological and immunological aspects of the disease, there may be some gain to be derived from a review and a re-evaluation of the histologic findings.

MATERIAL

More than one hundred cases of fatal falciparum malaria were studied at the Army Institute of Pathology during World War II. This study is based on the first fifty consecutive cases in which an autopsy protocol as well as sections, at least, of the principal organs were available for examination. In many of these cases, there was little more than a brief clinical note; this fact was not considered in selecting the cases since death often ensued relatively suddenly without previous illness and without sufficient time for clinical information to become available. However, further selection was made in that cases known to have had malaria previous to the fatal illness, to have been treated for malaria, or to have had any other chronic illness were not used for this study.

This series is comprised of soldiers from all Theaters of Operation who, presumably, so far as is known from the available information,

died in their first attack of falciparum malaria. The duration of illness was from one to fourteen days. These men were from 18 to 40 years of age; all but three were white; one was Mongolian (Chinese) and two were Negro (American). All but four cases had received either atabrine or quinine, usually only one to two doses administered at the time they were moribund; in the four cases not receiving therapy the cause of death was determined at the time of autopsy.

It is important to note that all but five (90 per cent) of the fifty patients were admitted to the hospital either in coma or with convulsions; three were admitted with diarrhea, and, of these, two were "mentally confused"; one was admitted with jaundice and diarrhea; and one had anuria after an illness of eight days.

Paraffin sections of all available organs were studied microscopically. The major portion of this study was based on the examination of hematoxylin-eosin stained paraffin sections although many of the tissues were also stained with Giemsa stain and by the method of Tomlinson and Grocott,² at times after removal of the parasite pigment with saturated picric-acid alcohol. Serial sections of the brain were made in several cases. Random cases were used for the study of the distribution of pigment (malarial and iron) by staining with potassium ferrocyanide and hydrochloric acid. Polaroid film was used to determine the refractility of pigments.

FINDINGS

Brain: Multiple sections, from five to twenty in each, were available for study in all cases. In 46 cases (92 per cent) there was engorgement of the cerebral capillaries. The entire capillary network of the brain in these cases was distended with erythrocytes (Fig. 3). In 41 of these 46 cases, there were large numbers of parasitized erythrocytes in the distended vessels whereas in the remaining five

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cases the erythrocytes were not parasitized. *Plasmodium falciparum* in all stages of development was present, although in the brain there was a predominance of young schizonts. The distended vessels were in all cases more prominent in the gray matter than in the white and they were evenly distributed in all locations. Pigmented parasites were found not only within erythrocytes but also were seen free in the lumen particularly of the larger vessels rather than in those of capillary size; the arteries were seldom distended. The distribution of parasitized cells in the capillaries was even and uniform and each vessel appeared to be equally distended and often occluded or "plugged" by the parasitized cells (Fig. 2 and 5). In the larger vessels, however, parasitized erythrocytes and parasites tended to hug the wall of the vessel to produce a "marginated" effect and often to form clumps at the periphery of the lumen (Fig. 6). The endothelial cells lining vessels of all sizes occasionally appeared hyperchromatic or swollen (Fig. 7) but no other reactive changes were noted. It was not possible to demonstrate that the endothelial cells possessed any phagocytic function either for pigment or for parasites, and only occasionally a rare pigmented phagocyte could be seen in a lumen.

In four cases no engorgement of cerebral vessels was noted nor was any remarkable number of parasites found in the brain or in other organs of these cases. One of the four patients died immediately following reaction to transfusion; another died suddenly and was found to have a pheochromocytoma of the adrenal; the third died after the administration of one dose of quinine, and the fourth developed anuria and hemoglobinuric nephrosis. The 41 cases in which the cerebral vessels were engorged with large numbers of parasitized erythrocytes showed a similar degree of parasitization of other viscera, such as heart, lungs and intestinal tract; similarly, in those cases in which parasites were not present in the brain, parasites were not demonstrated in other viscera, except, of course, in the spleen and liver where parasites and pigment always were present.

In fifteen (30 per cent) of the fifty cases multiple hemorrhages were present in the brain (Fig. 1); these lesions were associated in all cases with engorgement of the cerebral capillaries and in only one instance of hemorrhage were parasites not demonstrated in the brain. Clinically all the patients of this group were in coma on admission to the hospital and two had had convulsions. The distribution of the hemorrhages was identical in all instances although there was numerical variation: in the majority (12 cases) there were many hemorrhages; in two cases there were only a moderate number and in one case only two such lesions could be found in several sections studied. In all instances, these hemorrhages were in the subcortical white matter and not in the gray matter; they were also seen commonly in the pons, medulla and cerebellum. The spinal cord was not available for study in this series. The hemorrhages were identical in appearance in all locations and took the form of "ring hemorrhages" (Fig. 8) in which could usually be discerned a central vessel, "plugged" with erythrocytes which in all but one case were parasitized, or actually thrombosed. The tissue surrounding the central vessel was necrotic and there was demyelination of fibers (Fig. 11). The hemorrhage formed a round or oval zone immediately outside the central necrotic zone and was always separated from the central vessel by the distance of the zone of necrosis. It was not possible to demonstrate in any case that the origin of the hemorrhage was from the central vessel of the ring. Whereas in all but one case the number of parasitized erythrocytes in the brain was great and the lumens of the central vessels of the ring hemorrhages contained parasites, in no instance did the erythrocytes of the hemorrhage harbor plasmodium.

In addition to simple ring hemorrhages, twelve of the fifteen cases with these lesions showed also Durck's nodules,³ or the so-called malarial granulomas (Fig. 10). Every instance of "granuloma" in this series was associated with ring hemorrhages; in fact, the "granuloma" appeared actually to be an altered hemorrhage. These lesions consisted sim-

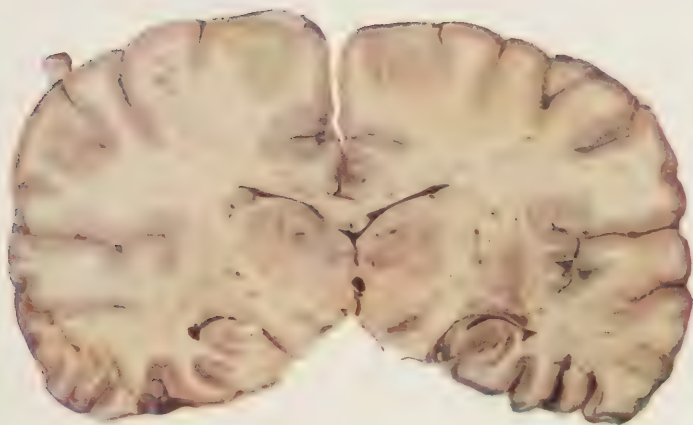


FIG.
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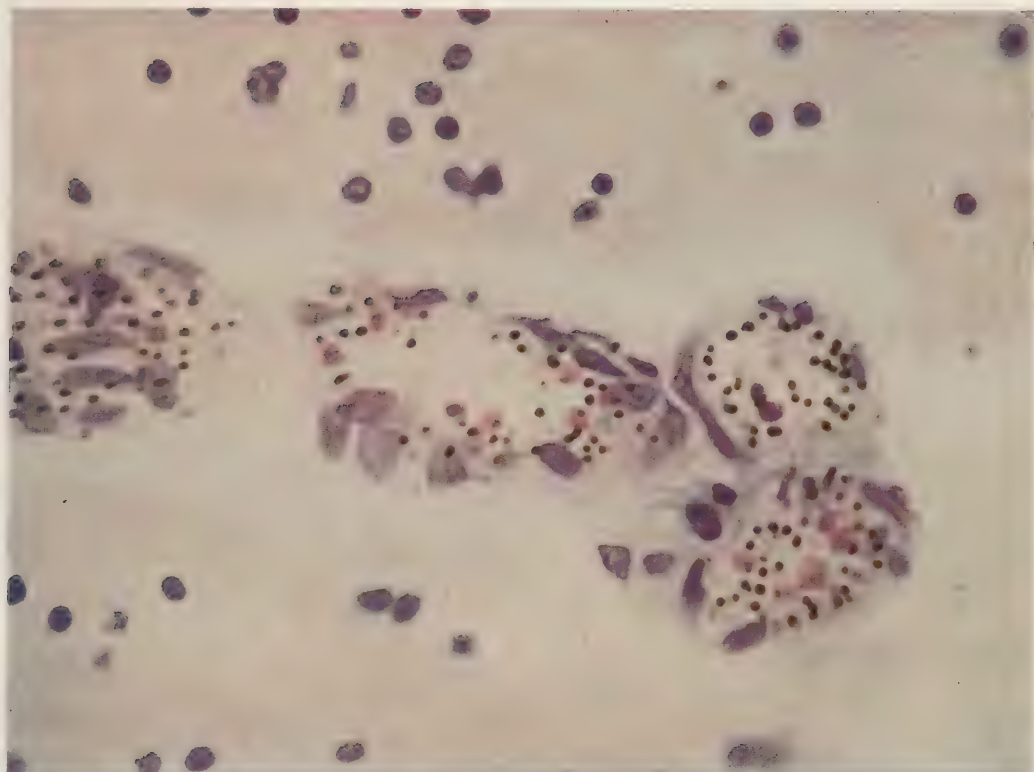


FIG.
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FIGURE 1. Sagittal section of brain of patient whose death was due to acute falciparum malaria. Cortex is grayer than normal and the subcortical white matter is studded with petechial hemorrhages. The so-called malarial granulomas are associated with these hemorrhages.

FIGURE 2. Capillaries of the brain are practically filled with parasites and parasitized erythrocytes; in the vessels of somewhat larger caliber there is "margination" of the parasites. X700.

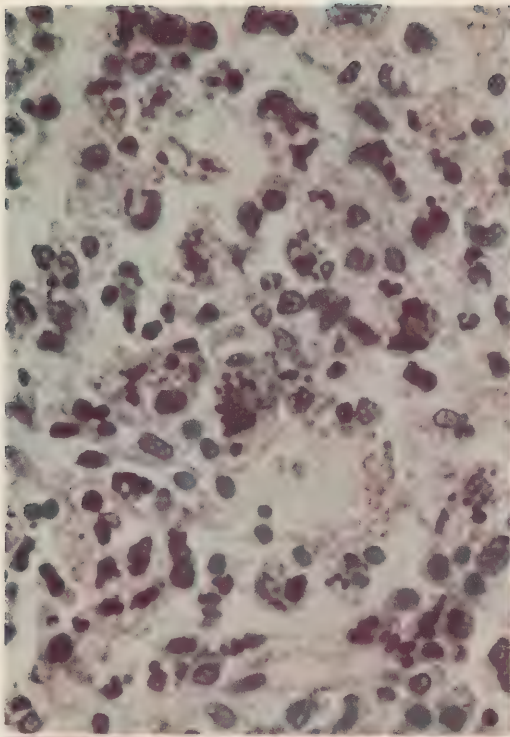


FIG.
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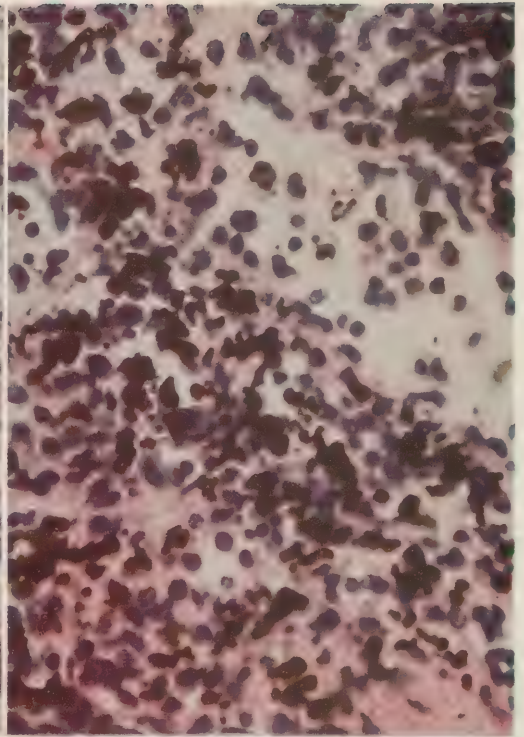


FIG.
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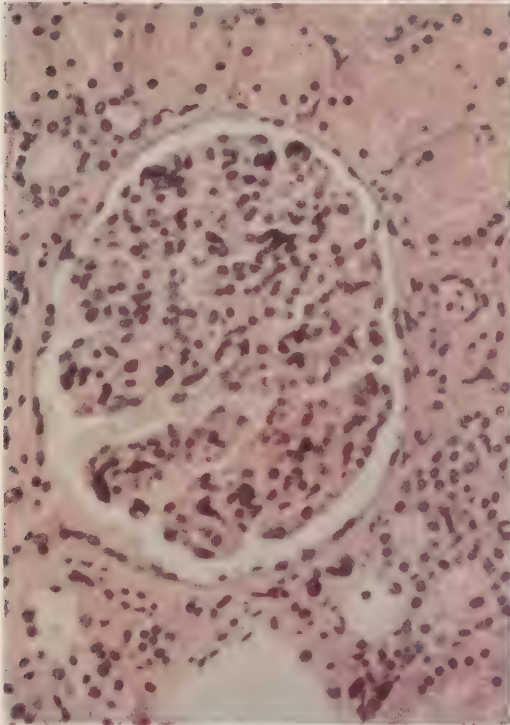


FIG.
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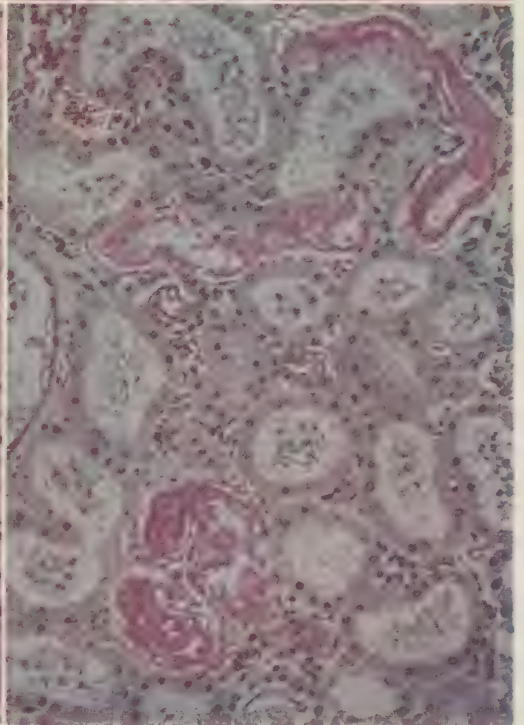


FIG.
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FIGURE 22. Spleen in acute falciparum malaria; pigment mostly as single grains. X700.

FIGURE 23. Spleen in chronic vivax malaria; pigment is coalesced and present intracellularly and extracellularly. Cords are fibrotic and sinuses are distended. X700

FIGURE 24. Kidney in acute falciparum malaria; pigmented phagocytes are trapped in the glomerular capillaries. Increased cellularity of the glomerulus. X350.

FIGURE 25. Hemoglobinuric nephrosis of acute falciparum malaria. Hemoglobin casts in distal convoluted tubules; necrosis and regeneration of tubular epithelium. X230.

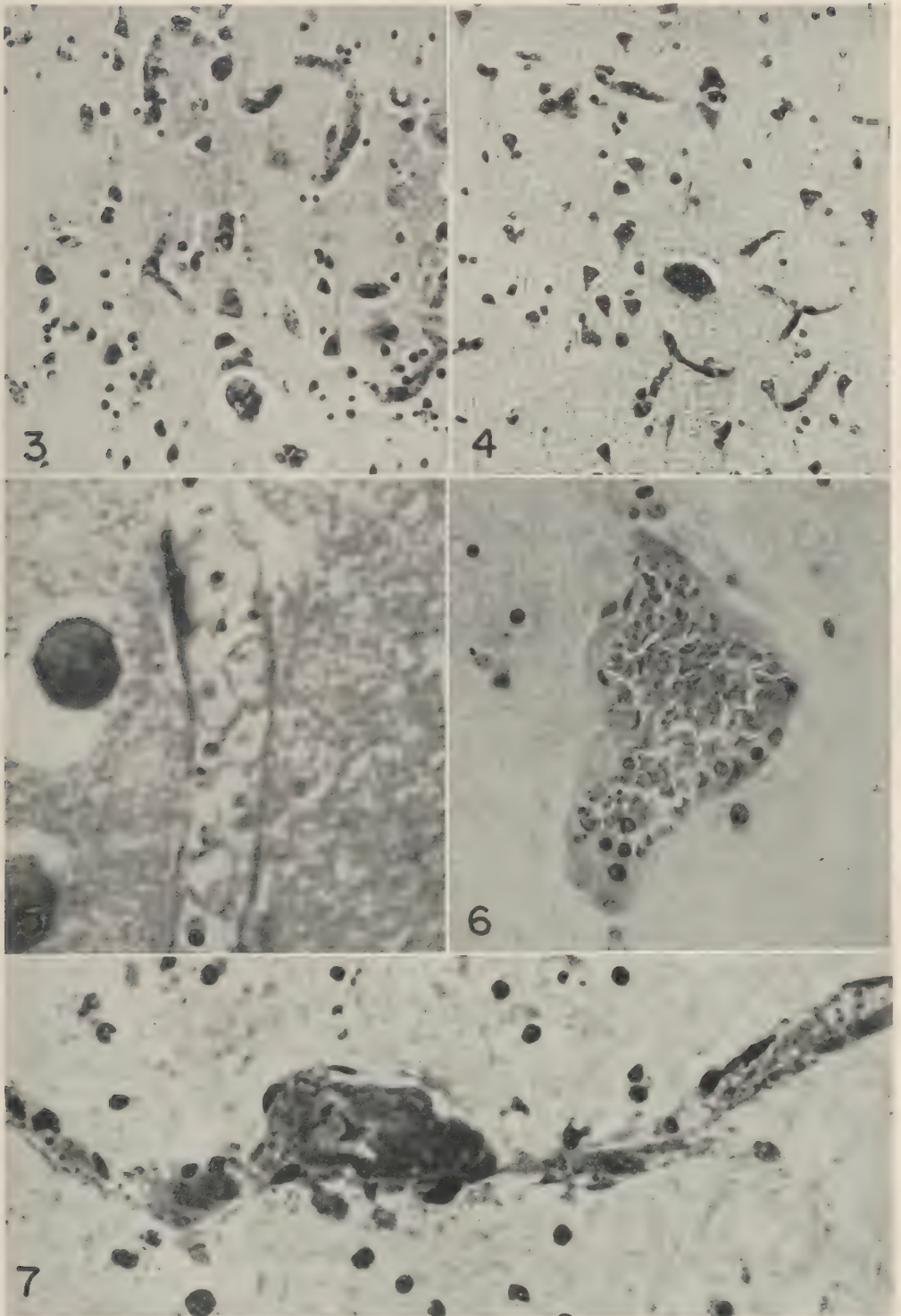


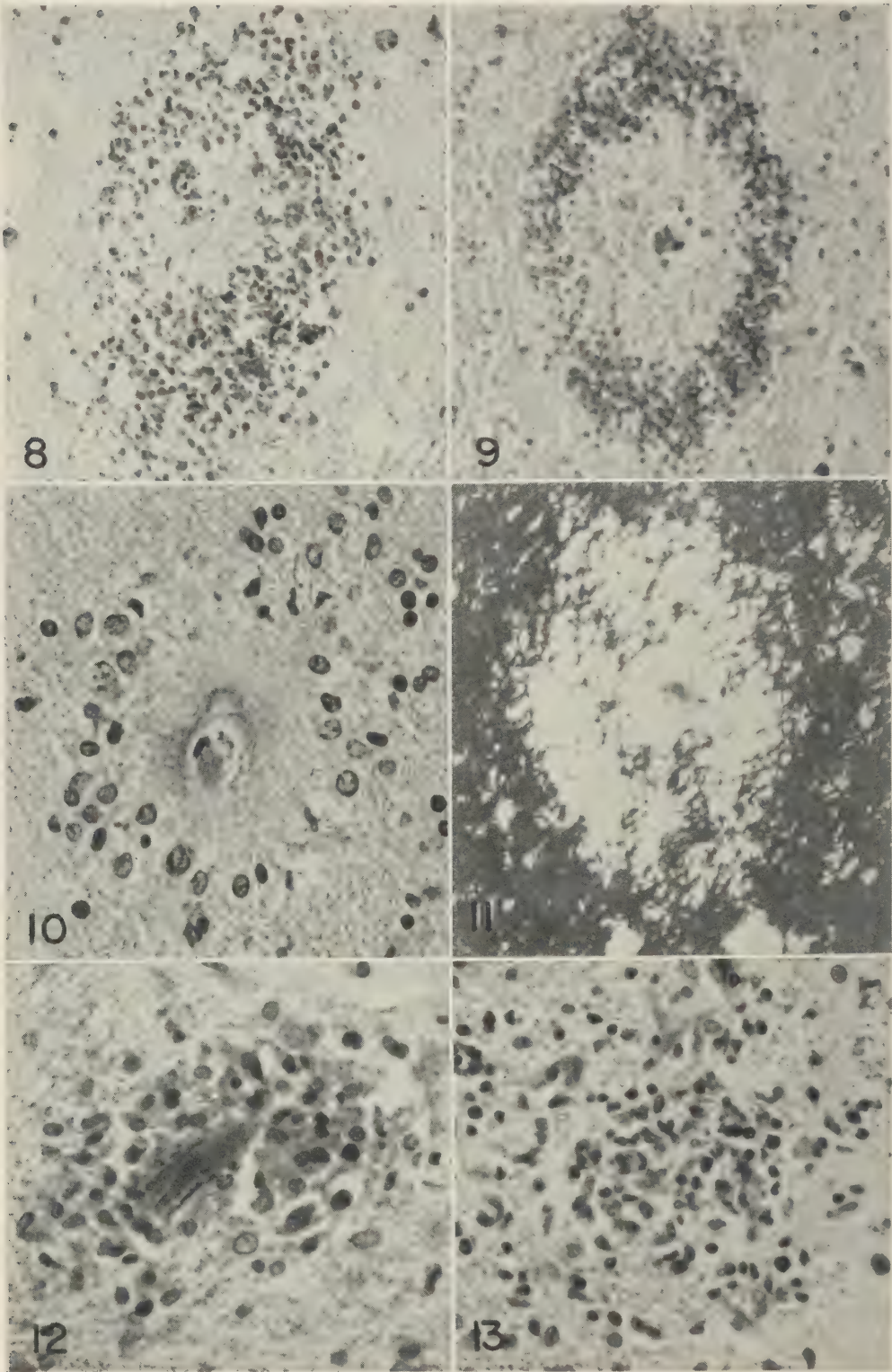
FIG. 3. Engorgement of cortical capillaries in acute falciparum malaria. AIP Neg. 89177 \times 230

FIG. 4. Engorgement of cortical capillaries occurring in high altitude anoxia. AIP Neg. 89175 \times 230

FIG. 5. "Plugging" of cortical capillaries by parasitized erythrocytes. AIP Neg. 77034 \times 2000

FIG. 6. Margination of parasitized erythrocytes in larger vessels. AIP Neg. 77351 \times 605

FIG. 7. Thrombosis of cerebral vessel associated with hemorrhage in other parts of the brain. Note the "plugging" of the vessel adjacent to the thrombosis. AIP Neg. 93672 \times 650



FIGS. 8-13

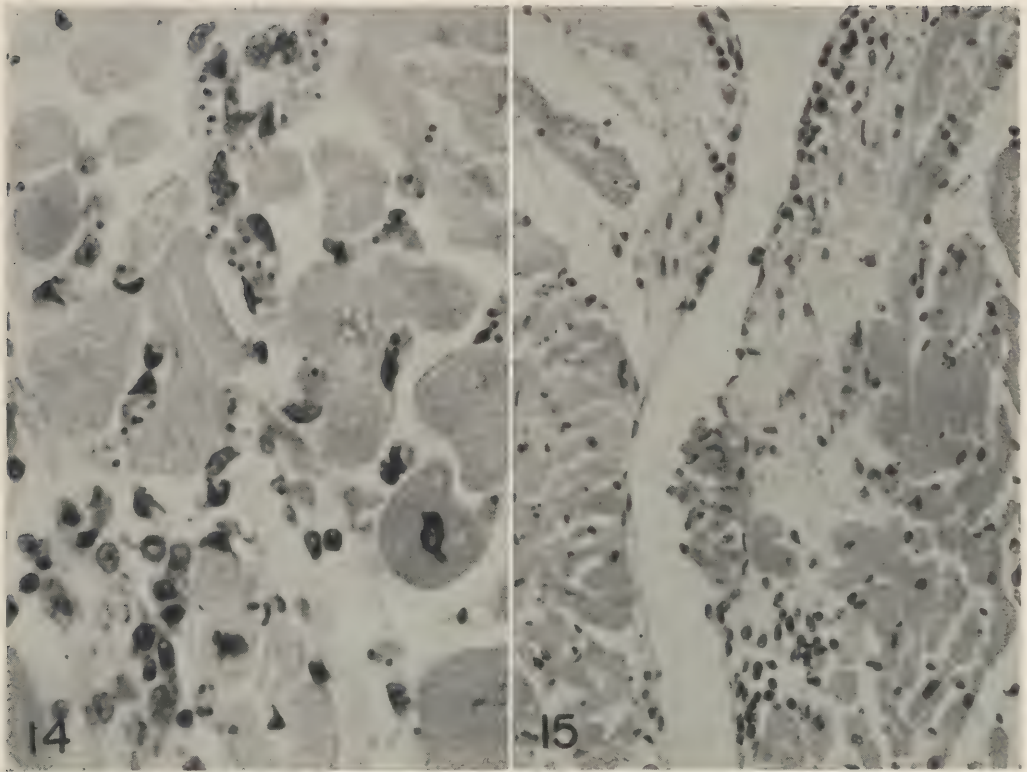


FIG. 14. Myocardium shows engorgement of capillaries equal to that seen in the brain. Interstitial infiltrate is composed of mononuclear cells. AIP Neg. 93669 $\times 650$

FIG. 15. Endocardial infiltrate and verrucae in acute falciparum malaria. AIP Neg. 88922 $\times 250$

ply of a single layered, or sometimes multiple layered, ring of neuroglial cells interposed between the hemorrhage and the necrotic zone surrounding the central vessel. In this series there was no instance of "granuloma" in which the necrotic zone was entirely filled in with neuroglial cells. It was thought that microglia were also present in the granuloma, but silver stains were of no benefit in the identification of the cells since the tissues submitted often had been fixed in formalin too

long for satisfactory staining. Although the hemorrhages were generally of the same size and presumably of the same age, the granulomas were not found at the site of every hemorrhage.

In the study of the "plugged," parasitized, vessels of the brain, it appeared that the lumens were not obstructed by parasitized erythrocytes but simply filled and distended by them, as if during life they were part of a moving stream. In the cases showing both

FIG. 8. Ring hemorrhage in brain of acute falciparum malaria. Note central "plugged" vessel, and necrotic intermediate zone. Erythrocytes of the hemorrhage are not parasitized. AIP Neg. 78510 $\times 330$.

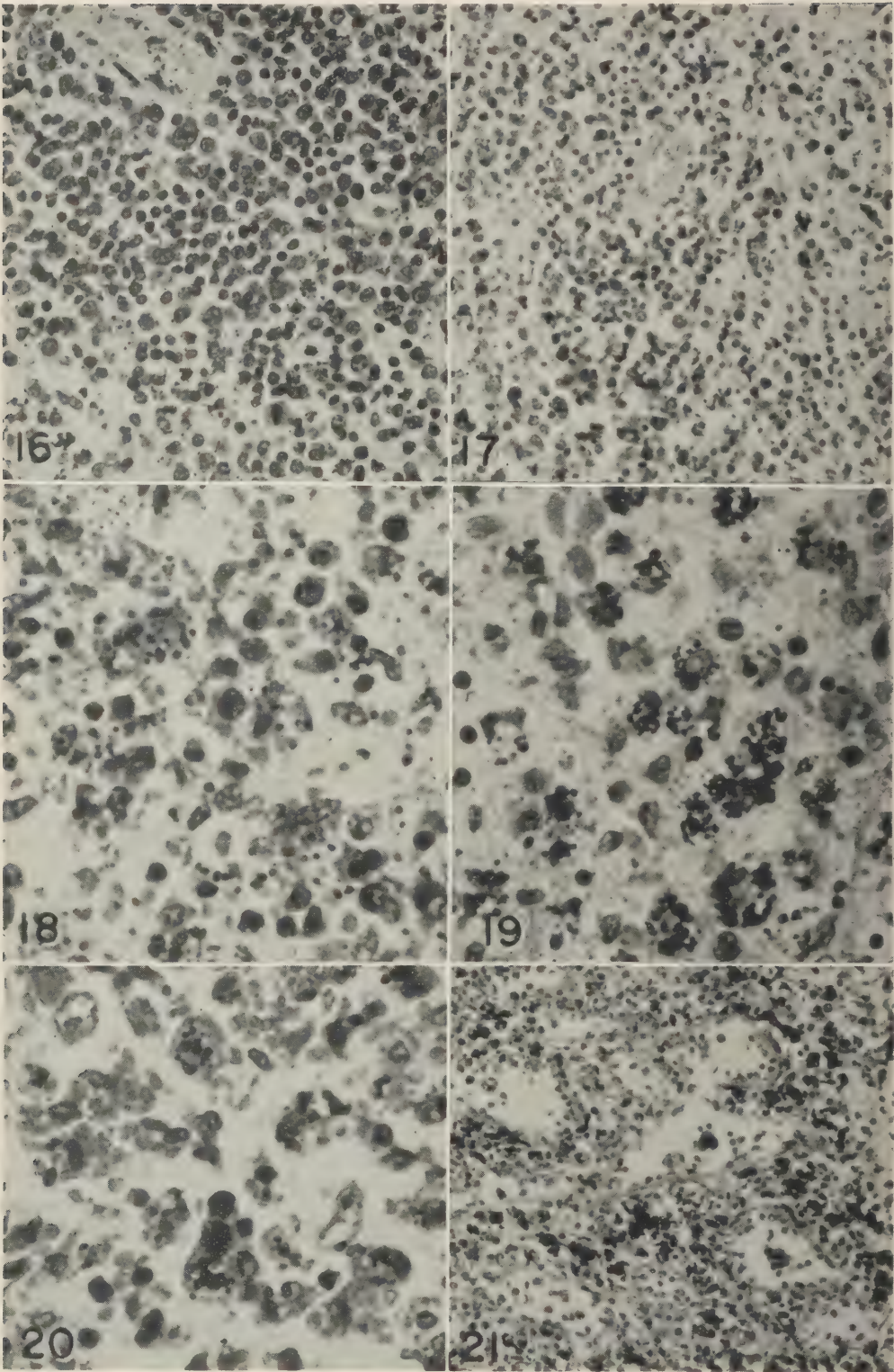
FIG. 9. Ring hemorrhage of brain in fat embolism similar to those found in falciparum malaria. AIP Neg. 89981 $\times 330$.

FIG. 10. Malarial "granuloma" composed of central thrombosed vessel, necrotic intermediate zone and peripheral rows of neuroglial cells mixed with nonparasitized erythrocytes. AIP Neg. 88928 $\times 500$

FIG. 11. Malarial "granuloma" showing demyelination in central necrotic zone. AIP Neg. 80929 $\times 500$

FIG. 12. Microinfarct of Rocky Mountain spotted fever, similar to the malarial "granuloma." AIP Neg. 82899 $\times 400$

FIG. 13. Inflammatory nodule of brain in Chagas' disease is in contrast to the noninflammatory "granuloma" of malaria. AIP Neg. 83009 $\times 450$



FIGS. 16-21.

hemorrhage and "granulomas," thrombi could be identified in the plugged vessels (Fig. 7), often in the central arteriole of the hemorrhage or "granuloma" but also in the capillaries at some distance from and unassociated with these lesions. Thrombi were also occasionally seen in the capillaries of the cortex. The thrombi were small, and usually distended a small segment of the otherwise "plugged" capillary or arteriole. Parasites, parasitized erythrocytes and pigment particles often completely encircled the thrombus but were not included in it. In other words, some thrombi were observed which did not completely occlude the lumens.

In addition to these lesions, other non-specific findings were noted in the brain. There were moderate to severe grades of satellitosis and neuronophagia in all cases showing parasitization, paralleling in each instance the degree of "plugging" of vessels and more prominent in those cases showing cerebral purpura. A few mononuclear cells were present in the edematous meninges and in the Robin-Virchow spaces of many cases. Pial edema was a prominent feature of all cases in which there were parasitization and engorgement of cerebral capillaries. A number of cases originating in the tropics, and therefore poorly preserved for purposes of critical study, showed certain effects of postmortem decomposition; namely, large vacuoles, particularly in the white matter of the brain, which often contained crystals of formalin pigment; and also, an irregular distribution of the Purkinje cells of the cerebellum so that for intervals the cells seemed to have fallen out or undergone a degenerative change.

Lungs: The degree to which parasites were present in the alveolar capillaries was found to be parallel to the concentration of parasites in the brain. Although dilatation and hyperemia of the septal capillaries was prominent in all lungs examined, in those which showed large numbers of parasites, these changes were extreme. Pulmonary edema was present in all. The parasitized erythrocytes were found in vessels of all sizes but were most prominent in the septal capillaries which were engorged with such cells often to the exclusion of others. Occasionally, considerable numbers of large pigmented phagocytes were found in the septal capillaries and were wedged tightly into the lumen. Thrombosis of vessels was not noted in the lungs. Small areas of hemorrhage were not uncommon in the lungs; the erythrocytes of these hemorrhages were, as in the brain, quite free of parasites. No infarcts were noted.

Pneumonia was found in 21 cases (42 per cent) and occurred as commonly in those cases in which parasites were few as in those in which large numbers of parasites were present. Fourteen (28 per cent) of these cases showed simple bronchopneumonia and in one of these multiple abscesses were present. The infiltrate in all but one case was not unusual; in the one case, however, in which the parasite concentration was high in all organs, the infiltrate was composed, for the most part, of polymorphonuclear leukocytes which contained many pigment granules. Phagocytosis of pigment and parasites in other organs (liver and spleen) was accomplished by mononuclear cells; moreover, in no other instance did the polymorphonuclear leukocytes exhibit evidence of the capacity for phagocytosis of pigment or

FIG. 16. Splenic follicle in falciparum malaria showing hyperchromatism of cells. Note parasitized cells in central artery, and phagocytosis of pigment by cells at the periphery of the follicle. AIP Neg. 78198 \times 500

FIG. 17. Almost complete depletion of splenic follicle occurring in a case of overwhelming falciparum infection. AIP Neg. 89875 \times 230

FIG. 18. Parasites and parasitized erythrocytes in splenic pulp. Few granules of pigment only in basophilic macrophages. AIP Neg. 93678 \times 650

FIG. 19. Marked phagocytic activity in macrophages of spleen. Each pigment granule is small, round and discrete. AIP Neg. 78195 \times 650

FIG. 20. Agglutination of pigment occurs within the macrophages in older cases. AIP Neg. 93679 \times 650

FIG. 21. Spleen of chronic recurrent vivax malaria showing distended sinusoids, fibrosis of cords and large amounts of agglutinated pigment. AIP Neg. 84312 \times 250

parasites. Only one case showed lobar pneumonia. In 6 cases (12 per cent) there was interstitial pneumonitis, of the type similar to that of "virus pneumonia," scrub typhus and several other diseases. This lesion was mild in four of the cases, consisting merely of septa thickened by mononuclear cells, a few of which were pigmented, and moderate numbers of these cells in the edema fluid of the alveoli. Two cases showed a more intense reaction that was accompanied by purulent bronchiolitis. These two cases were among those that exhibited renal lesions (hemoglobinuric nephrosis). The occurrence of interstitial pneumonitis in 12 per cent of this series is somewhat higher than that reported in Panama⁴ (3.7 per cent in military personnel).

In addition to these lesions, five of the cases showed a prominent hyaline membrane lining the alveoli. In none of these cases was there pneumonia; on the other hand, in all of them renal lesions (hemoglobinuric nephrosis) were present.

Heart: The concentration of parasites again was parallel to that seen in the brain and lungs. The myocardial capillaries were in 41 cases distended with parasitized erythrocytes. In these cases parasites were found also in larger vessels, particularly veins, hugging the walls of these vessels and forming mounds of parasitized erythrocytes. It was particularly noticeable in the heart that these mounds were often present along the same side of the walls of vessels rather than around the entire circumference. A similar finding was noted in the brain but was less conspicuous, and this uniform, eccentric settling of parasitized cells suggested that at least some of the clumping observed in the vessels might represent post-mortem phenomenon. In no case was there evidence of thrombosis of vessels of the heart, nor was there any case in which large numbers of parasitized erythrocytes were present in the large epicardial branches of the coronary arteries. One case showed moderate atheromatous changes in the intima of the left descending coronary artery and this was the

only case in which fibrosis of the myocardium occurred.

In forty-two of the cases (84 per cent) there was pronounced interstitial edema of the myocardium; the remainder were among those that showed few if any parasites. Edema was not localized to any one part of the heart. The muscle fibers were often widely separated by fluid but necrosis of the muscle fibers was not noted. In one case only was there myocardial fibrosis, and even in this instance the fibrosis was minimal. This was the case, noted above, associated with coronary sclerosis. Inasmuch as the fibrosis was obviously of long standing, it was considered to be pathogenetically unrelated to the acute infection with falciparum malaria. Three of the cases showed small, irregular subendocardial hemorrhages.

Interstitial myocardial infiltrate was present in 20 cases and was considered moderate in 11 cases and slight in 9 cases. The infiltrate was present exclusively in cases with high parasite counts and was irregular in distribution. Most often there were simply a few scattered foci of cells in the edematous interstitium. Occasionally there was infiltrate throughout a section. The cells of the infiltrate were in all instances mononuclear consisting of lymphocytes, plasma cells, Anitschkow myocytes and large macrophages (Fig. 14). Macrophages laden with pigment were not included in the infiltrate.

The myocardial infiltrate involved the endocardium in three of the more severe cases and in one case there were several small endocardial verrucae (Fig. 15). In only one case of this series was there pericarditis; this lesion was thought to be a complication of the associated lobar pneumonia.

Spleen: In contrast to other organs, the spleen and liver showed striking concentration of pigment, parasites, and parasitized erythrocytes. The degree of concentration of parasites in the spleen could not be correlated with the number of parasites in other viscera. The pigment present in the spleen was distinctly more abundant in those cases in which parasites were scarce in the brain; whereas, those

cases in which the parasite count of the brain was high showed less pigment, though many parasites, in the spleen.

In those cases with high parasite counts, parasitized erythrocytes were found in large numbers in the splenic arteries and generally in the veins as well although in smaller numbers. In the entire series, only four cases showed relatively few parasitized erythrocytes in the spleen; in the remainder there were large numbers. Parasites, parasitized erythrocytes and phagocytes were located predominantly in the red pulp although parasitized erythrocytes were also found in small numbers in the sinusoids. Both the Billroth cords and sinusoids were hyperemic. Fibrosis of the cords, so prominent in chronic malaria, was not noted in this group of acute cases.

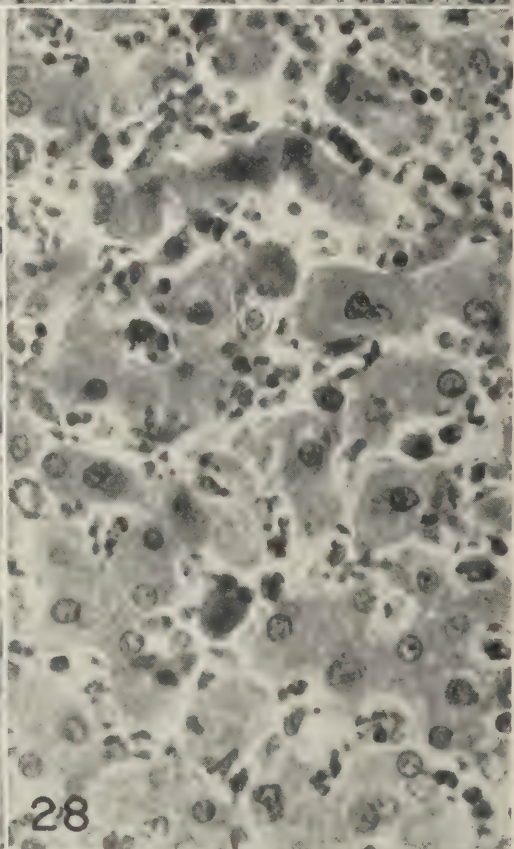
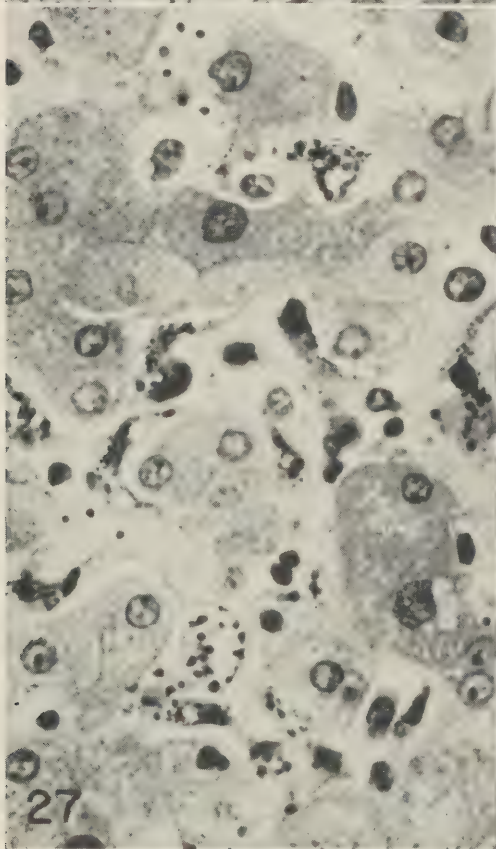
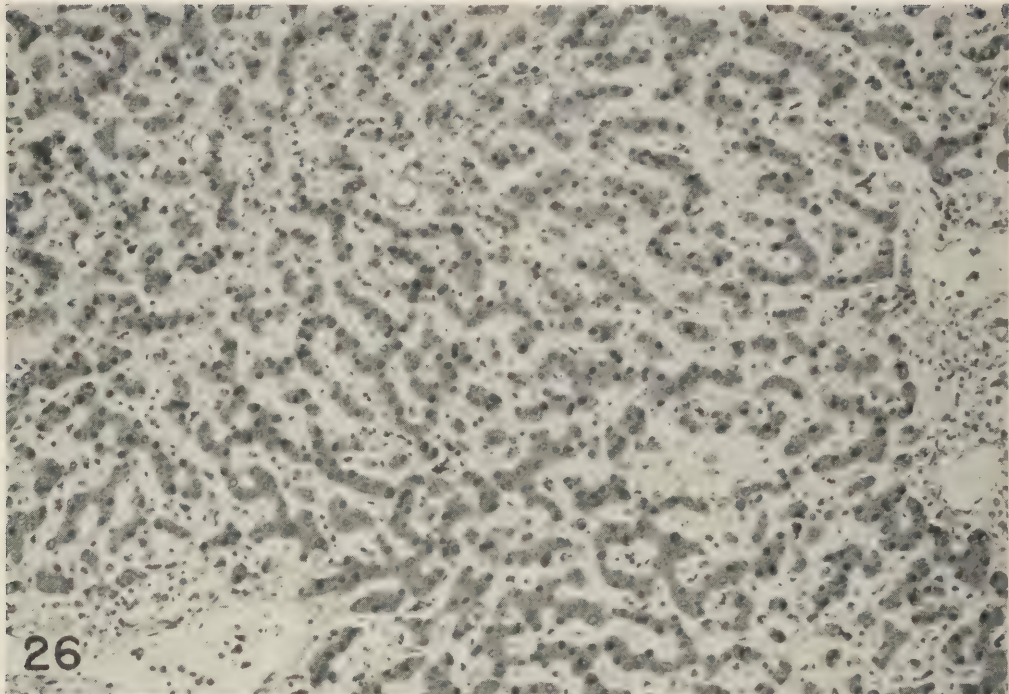
In approximately half the cases, a few central arteries showed the kind of hyaline swelling commonly found in spleens at autopsy. In almost all the cases, there were subintimal collections of cells in the trabecular veins. These cells had the morphology of extensions of white pulp and were so interpreted rather than as representing endophlebitis. This finding was not associated with thrombosis nor with any other unusual finding in the spleen and has been noted in routine autopsy material with approximately the same frequency. In only one was there an infarct which was small and fresh; it was not possible in the material available to identify thrombosis of an appertaining vessel.

The splenic follicles were variable in appearance. In 17 cases (34 per cent) the follicles were of normal size or somewhat larger than normal; in the remainder (66 per cent) they were distinctly smaller than normal. Of the 17 cases in the former group, three were among those that had the highest concentration of parasites in the viscera and relatively little phagocytic activity in the spleen; five had moderate numbers of parasites, and the remaining nine were those in which parasites were practically absent from the organs. Five of the cases showing follicles of normal or large size fell into the group also showing hemoglobinuric nephrosis.

The majority of cases (66 per cent) showed distinct diminution in size of follicles (Fig. 16) and in three of these no definite structure could be identified as follicle (Fig. 17). The edges of the follicles were no longer sharp but gradually merged into the red pulp. The cell components of the follicle were completely altered. Practically no small lymphocytes were present; instead, there were large cells of varying size and with hyperchromatic nuclei, which resembled lymphoblasts and basophilic macrophages (Fig. 16). Mitoses in these cells were frequent. Cells similar to those constituting the follicles, were also scattered in the cords and occasionally in the sinusoids where they frequently had phagocytosed pigment and parasites.

Both phagocytosed and free pigment was in all cases most concentrated in the Billroth cords. It was distinctly unusual to find phagocytosed pigment in any part of the follicle although occasionally a cell at the periphery of the follicle would contain a few grains (Fig. 16). Phagocytosis of pigment occurred in the red pulp by large phagocytic cells having both acidophilic and basophilic cytoplasm (Fig. 18). It was not uncommon to count in a single plane of section fifty or more granules of pigment in the cytoplasm of a single cell.

In this series, the larger amount of pigment was found as single round granules (Fig. 19). These granules were dark brown and could usually be distinguished from iron pigment, which might also be present in the same cells in considerable amounts, by the lighter color of the iron, and from formalin pigment, which was commonly present in the spleen, by the irregular, crystalline shape of the formalin. It was not possible to differentiate formalin pigment from parasite pigment on the basis of refractility since both were inconstantly refractile. In a moderate number of cases the malarial pigment was present also in small, black, conglomerate masses (Fig. 20) which occurred for the most part in macrophages but occasionally free in the red pulp as well. Only a relatively small number of pigmented macrophages escaped into the dilated sinusoids which, however, often contained large num-



FIGS. 26-28.

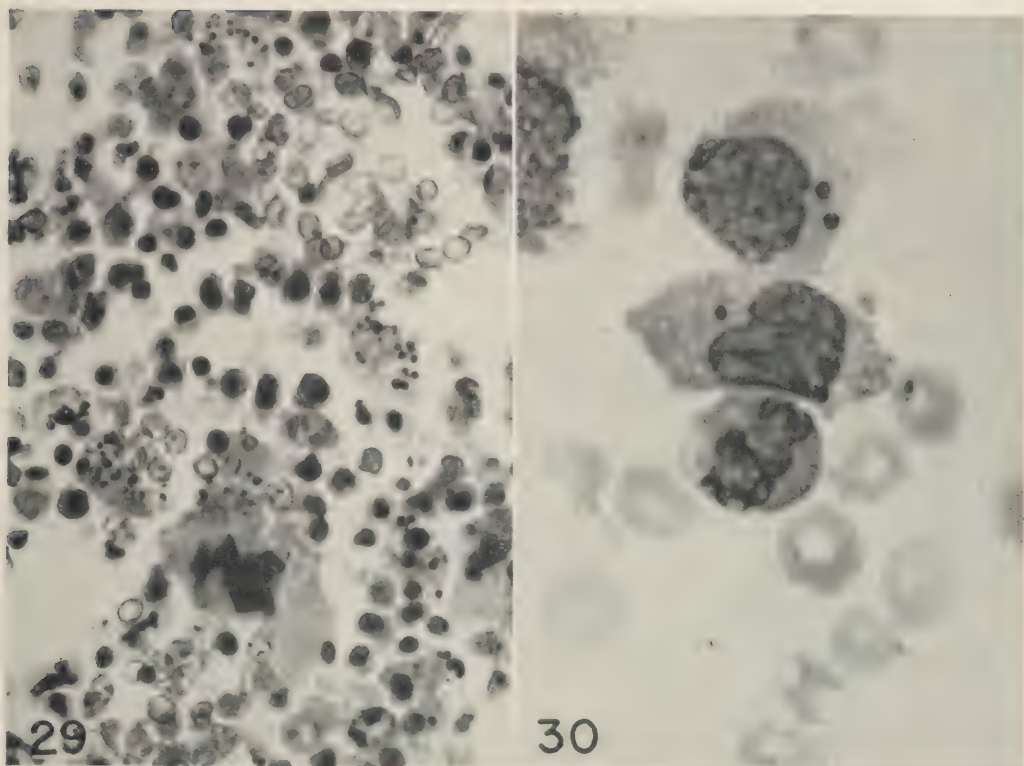


FIG. 29. Bone marrow of acute falciparum malaria. Phagocytosis of pigment and parasites is slight compared to spleen. AIP Neg. 78174 \times 700

FIG. 30. Peripheral blood of case of falciparum malaria; monocytes containing phagocytosed pigment are occasionally seen. AIP Neg. 85165 \times 1360

bers of parasitized erythrocytes. Infrequently a macrophage would seem to be adherent to the endothelial lining of the sinusoids but it was not possible to demonstrate that the endothelium possessed any phagocytic function.

Ten cases picked at random were stained both by the Giemsa and Tomlinson-Grocott methods for plasmodium. All forms of *Plasmodium falciparum* were present; segmenting schizonts and gametocytes were observed in greater numbers in the spleen than in the brain.

Liver: The changes in the liver, so far as phagocytosis of pigment is concerned, were parallel to, but less intense than, those in the spleen. The pigment was present for the most

part within the cytoplasm of the Kupffer cells which were often so crowded with pigment granules that they filled the sinusoids (Fig. 27). The sinusoids also contained varying numbers of parasitized erythrocytes. Pigment or parasites were not present in the hepatic parenchymal cells.

In 20 cases of this series there were collections of mononuclear cells in the portal areas but this finding could not be correlated either with clinical evidence of anemia or with the duration of the disease. In 17 cases, there was edema of the liver (Fig. 26). Fat was not prominent in the liver of any case. In 4 cases there was moderate central necrosis. Another

FIG. 26. Edema of liver in acute falciparum malaria. AIP Neg. 93677 \times 260

FIG. 27. Kupffer cells showing phagocytosis of large numbers of parasites and parasitized erythrocytes which can also be seen free in the sinusoids. AIP Neg. 93667 \times 650

FIG. 28. Early necrosis of liver in acute falciparum malaria as indicated by dark hyaline bodies in cytoplasm of hepatic and Kupffer cells. AIP Neg. 86375 \times 450

change of interest observed in 11 cases of the series was the occurrence of small, round, deeply acidophilic, hyalin-like bodies irregularly distributed through the liver, present both in parenchymal and Kupffer cells (Fig. 28). This lesions was associated with hepatic edema or focal frank necrosis of the cells of hepatic cords. Morphologically these bodies resembled the cytoplasmic inclusions found in

creased in number; erythroblasts were increased; megakaryocytes seemed to be more numerous than normal.

Kidney: Parasitized erythrocytes were present in the peritubular capillaries of the kidneys with the same constancy but in smaller numbers than in those of other organs; but only rarely were they seen in the glomerular capillaries. On the other hand, it was unusual

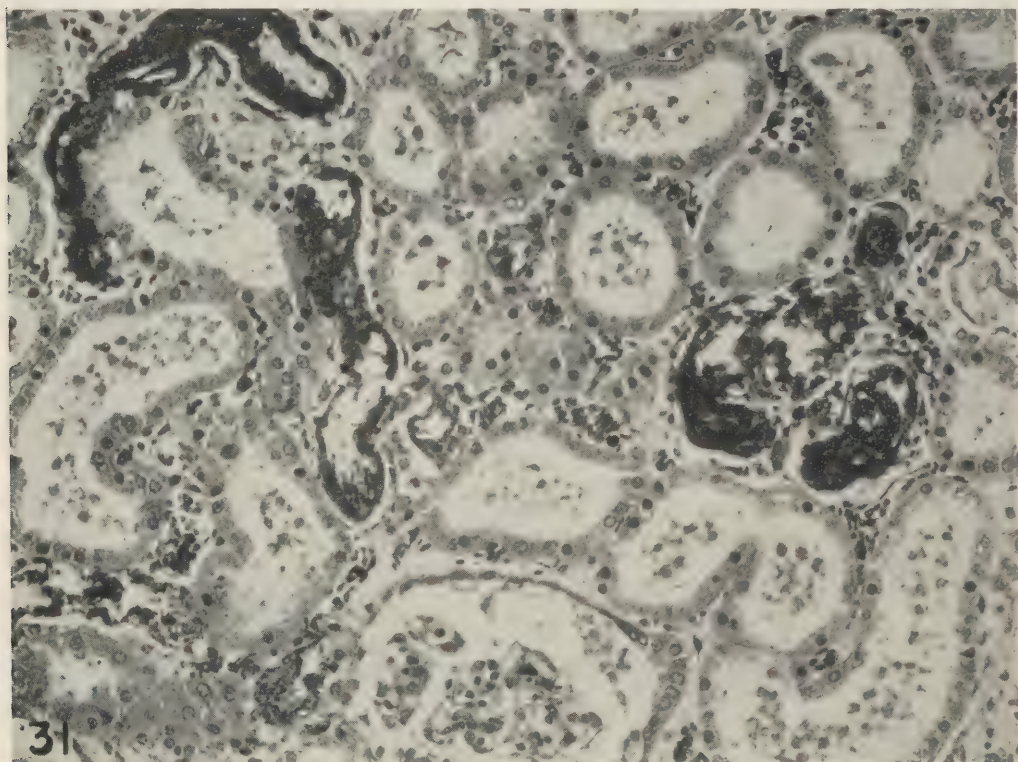


FIG. 31. Hemoglobinuric nephrosis in case of falciparum malaria. Pigmented casts in distal convoluted tubules associated with necrosis of tubular epithelium. AIP Neg. 93676 \times 260

yellow fever and were interpreted as evidence of early degeneration.

Bone Marrow: Parasitized erythrocytes were parallel to other organs in the bone marrow available in 18 cases (Fig. 29). The macrophages of the marrow were not as numerous as they were in the spleen; pigmented phagocytes were present but these cells contained fewer pigment granules and parasitized erythrocytes than similar cells in the spleen and liver. The marrow (either sternal or vertebral) was composed predominantly of mononuclear cells; granulocytes were de-

to find circulating phagocytes except within the glomerular capillaries where they seemed to be trapped in the lumens of these vessels (Fig. 24). In practically all cases the peritubular venules of the medulla contained large numbers of mononuclear cells; this finding showed no correlation with the degree of interstitial infiltrate or with any other lesion of the kidney.

Although pigmented casts were present in the lumens of a few of the distal convoluted tubules of 30 cases (60 per cent), hemoglobinuric nephrosis, of the type seen following

transfusion and in blackwater fever, was present in only 7 cases of this series (14 per cent). In these cases there were deeply pigmented casts in the distal part of the nephron, particularly in the distal convoluted and collecting tubules, associated often with necrosis and regeneration of the tubular epithelium (Fig. 31). In addition, there was dilatation especially of the proximal renal tubules, col-

organs, and in four there were parasitized cells only in the spleen. In five of these cases the splenic follicles were large. It is interesting that the only two Negroes of this group showed hemoglobinuric nephrosis.

In nine cases of this series (18 per cent), of which four also had hemoglobinuric nephrosis, there was definite glomerular alteration consisting of generalized ischemia, en-

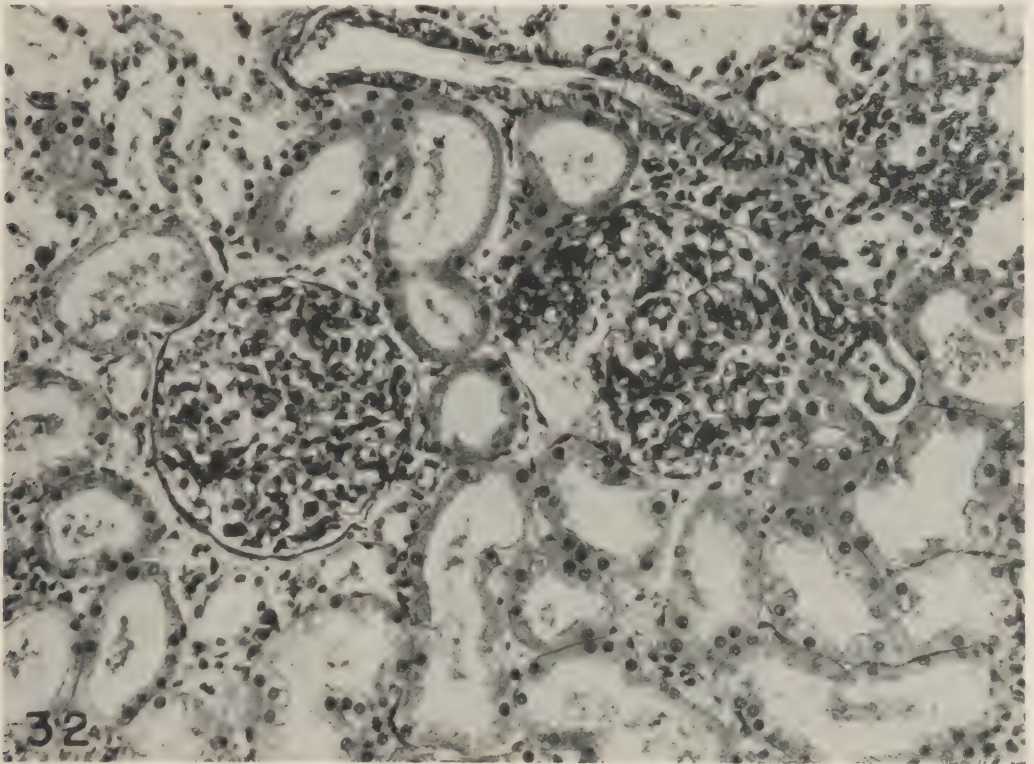


FIG. 32. Acute glomerulonephritis in falciparum malaria: glomerular ischemia, increased cellularity of glomerulus, hyperchromatism of endothelial cells, as well as vacuolization of epithelium of tubules. AIP Neg. 89176 \times 230.

lection of protein fluid and often hemoglobin in Bowman's spaces, interstitial edema and infiltration of lymphocytes, plasma cells, macrophages and occasional eosinophils. Endophlebitis was rare. In all of these cases there had been clinical evidence of renal insufficiency. In the only case in which transfusion had been given, the patient was already anuric and death occurred on the same day the transfusion was administered. Of these seven cases of hemoglobinuric nephrosis three showed large numbers of parasitized erythrocytes in all

largement and increased cellularity of the glomerulus, hyperchromatism and swelling of the endothelium, and occasionally thickening of the basement membranes (Fig. 32). Leukocytes were rarely found. Glomerulonephritis, of the type described above occurred in cases that had clinical evidence of azotemia; several of these cases showed also the hyaline membrane lining the pulmonary alveoli, the so-called uremic pneumonitis.*

* Personal communication of Dr. Tracy B. Malory.

In addition, in many of the cases, including those showing glomerulonephritis, the epithelium of the proximal convoluted tubules was swollen by cytoplasmic vacuoles. Three of the cases showed calcification of the epithelium of the distal convoluted tubules for no apparent clinical reason. Three cases showed moderate fibrinoid alteration of arterioles. In two cases there were a few acetylated sulfathiazole crystals in the lumens of the tubules although there was no associated inflammatory reaction in the kidney.

Gastrointestinal Tract: One to several sections of the gastrointestinal tract were available for study in 22 cases. In fifteen of these there was engorgement of the mucosal capillaries by parasitized erythrocytes. Hemorrhage into the mucosa was noted in only two cases unassociated with uremia, and submucosal edema was seen in three cases showing large numbers of parasites. Similar changes were present in two cases in which parasites were absent. Parasite concentration in the intestine was also parallel to that of other organs. It was interesting that only four of these cases had had diarrhea and that eleven cases showing equal numbers of parasites in the intestinal tract had not had symptoms referable to the intestine. No ulceration was noted, but one case in which sections of stomach were submitted showed diffuse gangrenous gastritis similar to that of mercury poisoning. The possibility of action by a poison could not be eliminated on the information available.

Pancreas: The pancreas was studied in approximately half the cases. Only one change was noted aside from the presence of parasitized cells in the capillaries to the same extent as in other organs. In six cases there was mild cystic dilatation of the pancreatic acini and ducts; two of these patients had had diarrhea, whereas the other four were in coma on admission.

Adrenals: The adrenals were available in all but eight cases. The concentration of parasitized erythrocytes was similar to that in other viscera; however, it did appear that there were greater numbers of pigmented phagocytes in the sinusoids of the adrenals than in other

organs. A moderate degree of degeneration of the fascicular cords was noted in twelve cases, all of which were admitted in coma; this lesion was marked in only one case in which bronchopneumonia was also present.

Lymph Nodes: Lymph nodes from unstated regions were studied in twelve cases. In general, parasites were found infrequently in the nodes even when they were present in large numbers in other organs. The marginal sinuses of several of these nodes were filled with mononuclear cells, similar to the basophilic histiocytes in other locations.

Other organs: Sections of testis, prostate, skeletal muscle and skin were present in some of the cases but showed no alterations of note.

DISCUSSION

"Localization of Parasites": From this series it appears that the majority of patients dying of acute uncomplicated falciparum malaria presents overwhelming infection of erythrocytes by plasmodium. Many of the cases would be classified in the category of "cerebral malaria," described and accepted by many authors, since 90 per cent of this group presented cerebral symptoms and many of these showed striking numbers of parasitized erythrocytes in the brain. Seyfarth⁵ has divided fatal falciparum malaria into several categories, of which the "septicemic" form accounts for 30 per cent and the "cerebral" form accounts for 55 per cent of the fatalities; the remainder are classified according to the "localization" of parasites in various viscera. In this series "localization" or concentration of parasites occurs only in the spleen, liver and bone marrow and parasitized erythrocytes in other organs, including the brain, have been found to be otherwise uniformly distributed. In other words, if the infection is heavy, there are equal numbers of parasitized cells in the capillaries of such organs as the brain, heart, lungs and intestinal tract, although the clinical symptoms may point to one organ primarily. If the infection is light, the distribution of parasitized cells is similarly uniform and generalized. The theory of *selective localization* of parasitized

cells, then, cannot account for the varied clinical phenomena so characteristic of fatal falciparum malaria.

Pigment: Although striking numbers of parasitized erythrocytes and parasites are found in the vessels of all organs and although an occasional circulating pigmented phagocyte may be seen in the capillaries of any organ or may even appear in the peripheral blood (Fig. 30), the bone marrow, liver and spleen are clearly the depositories of malarial pigment (Fig. 14-21, 24-27). Taliaferro^{6,7} has emphasized that the death of parasites is accomplished by the phagocytosis of free parasites and parasitized erythrocytes by existing and new macrophages in situations where the blood flows slowly and comes into intimate contact with such cells. The most intense phagocytosis is therefore seen in the spleen, to a certain extent in the liver, and least of all in the bone marrow. Endothelial cells lining vessels do not exhibit the power to phagocytose pigment of malarial parasites, notwithstanding their capacity to phagocytose granules of supravital injected dyes. Macrophages, capable of phagocytosing pigment, are already present in large numbers in these organs prior to infection. While these cells multiply during the infection (Fig. 16) they are not the only source of phagocytes inasmuch as other cells are activated to produce new macrophages (Fig. 16), particularly in the spleen where, as Taliaferro and Cannon⁸ have shown, the direct transformation of lymphocytes into macrophages occurs. In the suppression of the infection, the parasites and parasitized erythrocytes are held in the Billroth cords of the spleen by the newly developed macrophages probably by means of a specific agglutinative substance which develops at the surfaces of these cells (Cannon⁹). The lymphocyte is of great importance in malarial infections not only from the standpoint of its evolution into macrophages, but also on account of its major role in the transportation of antibodies.¹⁰ Here, too, as in the typhus fevers and in other infections characterized by a lymphocytosis of the peripheral blood, the problem must be further clarified by multiple correlations of antibody

levels, peripheral lymphocytosis, and tissue lymphocytosis.

Both malarial and iron pigments were found in the macrophages. Malarial pigment consists of small round dark brown granules which in the majority of cases are discrete globules of somewhat varying size (Fig. 18, 19 and 22). The smaller granules which represent the pigment of the early schizonts appear a lighter brown color than the darker, somewhat larger granules of the older parasites. In some of the cases there is agglutination of the single pigment granules into irregular masses of pigment which are almost black (Fig. 20). This agglutination of pigment probably indicates longer duration of the infection (Cannon⁹). The smaller pigment granules are usually within the cytoplasm of macrophages while the agglutinated masses of pigment may be found extracellularly.

Although the sinusoids are dilated in these cases, the infection had not existed for periods long enough to produce the striking fibrosis often noted in cases of chronic vivax malaria (Fig. 21 and 23) nor did they show the acute congestion of the ruptured spleen of acute vivax malaria, of which there were six examples available for study at the Army Institute of Pathology.

Pigment that could be stained for iron was often present within the same macrophages that contained parasite pigment. Rigdon¹¹ suggests, from experimental evidence, that malarial pigment, ferrihemate or hemozoin (Morrison and Anderson¹²), which can not be stained for iron, may be gradually oxidized into an iron-containing pigment which may then be utilized by the body, thus accounting for its gradual disappearance. This evidence is convincing although some of the iron-containing pigment in malaria undoubtedly results from the destruction of erythrocytes during the cyclic development of the parasite.

Except for its morphology and failure to stain for iron, malarial pigment is difficult to distinguish from other pigments. Although Cowdry¹³ makes the interesting observation that malarial pigment is doubly refractile, this feature was not found to be constant in our

fixed, stained tissues; and in addition, formalin pigment, so often present in these tissues, is also occasionally refractile, which further diminishes the usefulness of this criterion.

Consideration of the Pathogenesis of Cerebral Lesions: The most constant finding in the brains of this series of acute fatal falciparum malaria is the intense engorgement of cerebral capillaries (Fig. 3) either in the complete absence of or in association with parasitization of erythrocytes. The precise mechanism of the engorgement is not clear but such factors as stagnation of blood in the capillaries, thromboses, and anoxia from other causes are probably concerned. Certainly a similar picture of extreme engorgement of cerebral capillaries is seen following anoxia due to flying in high altitudes (Fig. 4).

In any case it appears obvious that factors other than the simple "plugging" of the capillaries by parasitized cells must exist to explain the cerebral symptoms which so often characterize this disease. Rigdon,¹⁴ Kean and Smith¹⁵ and others have suggested that these symptoms may be related to shock. The signs of shock are noted also in this series. However, the explanation of the pathogenesis of shock is no less simple in acute falciparum malaria than in other infections and conditions. From the point of view of the morphologist, the stagnation of the capillary blood flow due to the presence of parasitized red blood cells of increased density, and perhaps viscosity, the effects of toxemia on capillary tone, the role of the adrenal gland (Rich¹⁶), the effect of involvement of important cerebral centers, are all possible single or multiple factors in the production of the overall picture of shock. In these acute cases, anemia was not present to a degree sufficient to account for significant anoxia.

The occurrence of cerebral hemorrhages (Fig. 1 and 8) and the so-called granulomas (Fig. 10 and 11) in 30 per cent of these cases is explained on the basis of thrombosis (Fig. 7 and 10). Anderson and Morrison¹⁷ have recorded widespread thromboses in monkeys with simian malaria and by the injection of ferrihemate (parasite pigment) but

explain these findings on the basis of anoxia related to anemia; they also disclaim malarial pigment as the specific toxic factor since it is not liberated in soluble form from the parasite. It is clear that in malaria, the hemorrhages and granulomas, which are actually minute infarcts, are identical with those same lesions found in brain purpuras from a variety of other causes, for example fat embolism (Fig. 9) and spotted fever, (Fig. 12) in which the vessels of the brain are occluded either by emboli as in the former, or by thrombi as in the latter.

Vance¹⁸ has offered a clear and logical explanation for the localization of these hemorrhagic lesions in the white matter of the brain (Fig. 1) rather than in the cortex. He states that although emboli (of fat) are present in the cortex, lesions can not be demonstrated since "the capillary anastomoses are so extensive that the nutrition of the tissue is rarely impaired. . . . In the white matter the situation is different. The arterioles are end-vessels which branch in a dendritic fashion and which communicate by scanty capillary anastomoses. The embolus obstructing such a vessel effectively impairs the nutrition of the tissue it supplies and degenerative changes occur."

The ring form of the hemorrhage is also common to other cerebral purpuras, and it is generally conceded that the source of the hemorrhage is not from the occluded central vessel but from the surrounding capillaries which are not occluded. The "granuloma" is interpreted as part of the process of repair whereby the necrotic zone is more or less replaced with glial cells, rather than as an inflammatory nodule provoked by toxins or parasites such as occurs in toxoplasmosis and trypanosomiasis (Fig. 13). The fact that the "granulomas" were always found to be associated with hemorrhage and that solid nodules unassociated with hemorrhage, such as those described by Dhayagude and Puranare,¹⁹ were not found, is undoubtedly due to the short duration of the disease in this series.

Other Thrombotic Lesions: It has been possible in this series of cases to demonstrate thrombosis only in the cerebral vessels of small

calibre. Only one infarct of the spleen was noted in this group, whereas the subendothelial proliferation of the white pulp to which splenic infarcts have been attributed²⁰ was found in practically all the cases. Therefore, the mere intimal location of these cells cannot be regarded as the cause of these infarcts. Likewise, the capillaries of the heart also contained large numbers of parasitized erythrocytes whereas the larger branches of the coronary arteries were not similarly "plugged." The only example of myocardial infarction in this series was of long duration and related to coronary sclerosis rather than the acute malaria, contrary to the interpretation of recent reports.²¹

Hepatic Dysfunction: Changes other than concentration of parasites and malarial pigment in the liver occur in falciparum malaria. Edema was noted regularly (Fig. 26), central necrosis occasionally, and in a significant number of cases there was evidence of early necrosis (Fig. 28). Clinical evidence of hepatic dysfunction in malaria has been reported by Nursky, von Brecht and Williams²² and similar dysfunction may have been present in these patients with falciparum malaria. However, it does not seem justifiable to conclude that the histologic evidence warrants the assumption that hepatic dysfunction existed. In addition, it would appear that these changes could be completely reparable since widespread destruction of the parenchyma did not occur.

Renal Complications: Conflicting statements are found in the literature regarding the incidence of nephritis in malaria. In chronic malaria, particularly in the recurrent malariae malaria, the incidence of nephritis associated with the clinical complex of lipoid nephrosis is high (Menon and Annamalai²³ and Giglioli²⁴). Nephritis in acute malaria is said to be rare except in the fatal forms (Seyfarth⁵). In this series, glomerulonephritis occurred in 18 per cent of cases. This type of intracapillary glomerulonephritis (Fig. 32) is that which is found in other infections such as scarlet fever and the typhus fevers,²⁵ and, as in these latter infections, is regarded as a toxic, or, more likely, an allergic manifestation. These lesions have been produced experimentally in

dogs²⁶ and monkeys¹⁷ by inoculation of ferrihemate and by the production of experimental malaria. Again, as in the typhus fevers so with the malarias, much experimental work needs to be done from the point of view of determining the histologic effect of various toxins and allergens of the rickettsiae as well as the plasmodia on the kidney and other organs.

Blackwater fever is a well known complication of falciparum malaria particularly in recurrent infections and after quinine therapy. The pathologic findings in blackwater fever are identical with those of hemoglobinuric nephrosis due to a variety of other causes such as the crush syndrome, incompatible transfusion, and other hemolytic diseases. The occurrence of hemoglobinuric nephrosis in 14 per cent of the cases of acute falciparum malaria of this series is unexpectedly high since there were not other factors except the malaria itself by which to explain this phenomenon. The occurrence of "blackwater fever" in acute malaria, as well as after recurrent attacks and after therapy, may then be considered as related to the hemolysis which may be extreme in cases of overwhelming infection with *Plasmodium falciparum*. The precise immunologic or mechanical basis for this phenomenon remains to be clarified. It is of interest that four of the cases of hemoglobinuric nephrosis were associated with early acute diffuse glomerulonephritis. This is to say that in a considerable proportion of instances of hemoglobinuric nephrosis due to malaria, the glomerular dysfunction is an important factor in the production of the signs and symptoms of renal insufficiency.

SUMMARY

1. The pathologic lesions in 50 cases of fatal falciparum malaria are presented and correlated with clinical information available.

2. *Selective* localization of parasitized erythrocytes does not occur outside the bone marrow, liver and spleen; the presence of "plugged" parasitized vessels in an organ can not be correlated with clinical symptoms.

3. Cerebral symptoms are considered to be

related to anoxia since the lesions found in anoxia from other causes are present in identical form in the brain of falciparum malaria.

4. Thrombosis of the cerebral vessels is frequent, causing hemorrhages and the so-called granulomas. Thrombotic lesions are not present in other organs of this series.

5. Renal lesions, both diffuse glomerulonephritis and hemoglobinuric nephrosis, occur with relative frequency and are, together with the myocardial infiltrate and adrenal "atrophy," evidence in favor of circulating toxins or allergens, probably released by the *Plasmodium falciparum*.

REFERENCES

- ¹ Helpern, M.: Epidemic of Fatal Estivo-autumnal Malaria. *Am. J. Surg.* 26: 111-123, 1934.
- ² Tomlinson, W. J., and Grocott, R. G.: Simple Method of staining Malaria Protozoa and Other Parasites in Paraffin Sections. *Am. J. Clin. Path.* 14: 316-326, 1944.
- ³ Dürck, H.: Über die bei Malaria pernicioso comatosa auftretenden Veränderungen des Zentralnervensystems. *Arch. f. Schiffs. u. Tropenhyg.* 21: 117-132, 1917.
- ⁴ Applebaum, I. L., and Schrager, J.: Pneumonitis Associated with Malaria. *Arch. Int. Med.* 74: 155-162, 1944.
- ⁵ Seyfarth, C.: Die Malaria. In Henke, F., and Lubarch, O. *Handbuch der speziellen pathologischen Anatomie und Histologie.* 1: 178-248. Berlin, Springer, 1926.
- ⁶ Taliaferro, W. H., and Mulligan, H. W. The Histopathology of Malaria with Special Reference to the Function and Origin of the Macrophages in Defense. *Indian M. Research Mem.* 29: 1-138, 1937.
- ⁷ Taliaferro, W. H.: Immunity in Malaria. *Am. J. Clin. Path.* 14: 593-597, 1944.
- ⁸ Taliaferro, W. H., and Cannon, P. R.: Cellular Reactions during Infections and Superinfections of *Plasmodium brasilianum* in Panamanian Monkeys. *J. Infect. Dis.* 59: 72-125, 1936.
- ⁹ Cannon, P. R.: Some Pathologic Aspects of Human Malaria: A Symposium on Human Malaria. *Pub. of A.A.A.S.* 15: 214-220, 1941.
- ¹⁰ Dougherty, T. F., Chase, J. H., and White, A. Demonstration of Antibodies in Lymphocytes. *Proc. Soc. Exper. Biol. & Med.* 57: 295-298, 1945.
- ¹¹ Rigdon, R. H.: Malarial Pigment. *Am. J. Clin. Path.* 15: 489-493, 1945.
- ¹² Morrison, D. B., and Anderson, W. A. D.: The Pigment of the Malaria Parasite. *Pub. Health Rep.* 57: 90-94, 1942.
- ¹³ Cowdry, E. V., and Scott, G. H.: Études cytologiques sur le paludisme; mitochondries, granules colorables, au rouge neutre et appareil de Golgi. *Arch. Inst. Pasteur de Tunis.* 17: 233-252, 1928.
- ¹⁴ Rigdon, R. H.: A Consideration of the Mechanism of Death in Acute *Plasmodium falciparum* Infection. *Am. J. Hyg.* 36: 269-275, 1942.
- ¹⁵ Kean, B. H., and Smith, J. A.: Death Due to Estivo-autumnal Malaria. *Am. J. Trop. Med.* 34: 379-381, 1944.
- ¹⁶ Rich, A. R.: A Peculiar Type of Adrenal Cortical Damage Associated with Acute Infections and Its Possible Relation to Circulatory Collapse. *Bull. Johns Hopkins Hosp.* 74: 1-15, 1944.
- ¹⁷ Anderson, W. A. D., and Morrison, D. B.: Role of Parasite Pigment (Ferrihemic Acid) in the Production of Lesions in Malaria. *Arch. Path.* 33: 677-686, 1942.
- ¹⁸ Vance, B. M.: The Significance of Fat Embolism. *Arch. Surg.* 23: 426-465, 1931.
- ¹⁹ Dhayagude, R. G., and Puranare, N. M.: Autopsy Study of Cerebral Malaria with Special Reference to Malarial Granuloma. *Arch. Path.* 36: 550-558, 1943.
- ²⁰ Rigdon, R. H.: A Consideration of the Mechanisms of Splenic Infarcts in Malaria. *Am. J. Trop. Med.* 24: 349-354, 1945.
- ²¹ Merkel, W. C.: *Plasmodium falciparum* Malaria. *Arch. Path.* 41: 290-298, 1946.
- ²² Mirsky, I. A., von Brecht, R. and Williams, L. D.: Hepatic Dysfunction. *Science.* 99: 20-21, 1944.
- ²³ Menon, T. B., and Annamalai, D. R.: Nephrosis in Malaria. *J. Trop. Med.* 36: 379-381, 1933.
- ²⁴ Giglioli, G.: Clinical Notes, Autopsy and Histopathological Findings from Five Cases of Quartan Malarial Nephritis from British Guiana. *Trans. Roy. Soc. Trop. Med. & Hyg.* 26: 177-187, 1932.
- ²⁵ Allen, A. C., and Spitz, S.: A Comparative Study of the Pathology of Scrub Typhus (Tsutsugamushi Disease) and other Rickettsial Diseases. *Am. J. Path.* 21: 603-681, 1945.
- ²⁶ Anderson, W. A. D., Morrison, D. B., and Williams, E. F., Jr.: Pathologic Changes Following Injections of Ferrihemic (Hematin) in Dogs. *Arch. Path.* 33: 589-602, 1942.

TUMORS OF THE TESTIS*

A REPORT ON 922 CASES

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(With thirty-one illustrations)

THIS paper deals first, with the classification, architecture and morphogenesis of testicular tumors, and second, with the biologic behavior of the different types, as evidenced by the incidence and cellular composition of metastases, the evolution of struc-

of Pathology between October 1940, when selective service began, and May 1946. The tumors were obtained from a relatively homogeneous group, since most of the patients were of military age (18-38) and were serving in the Army of the United States.

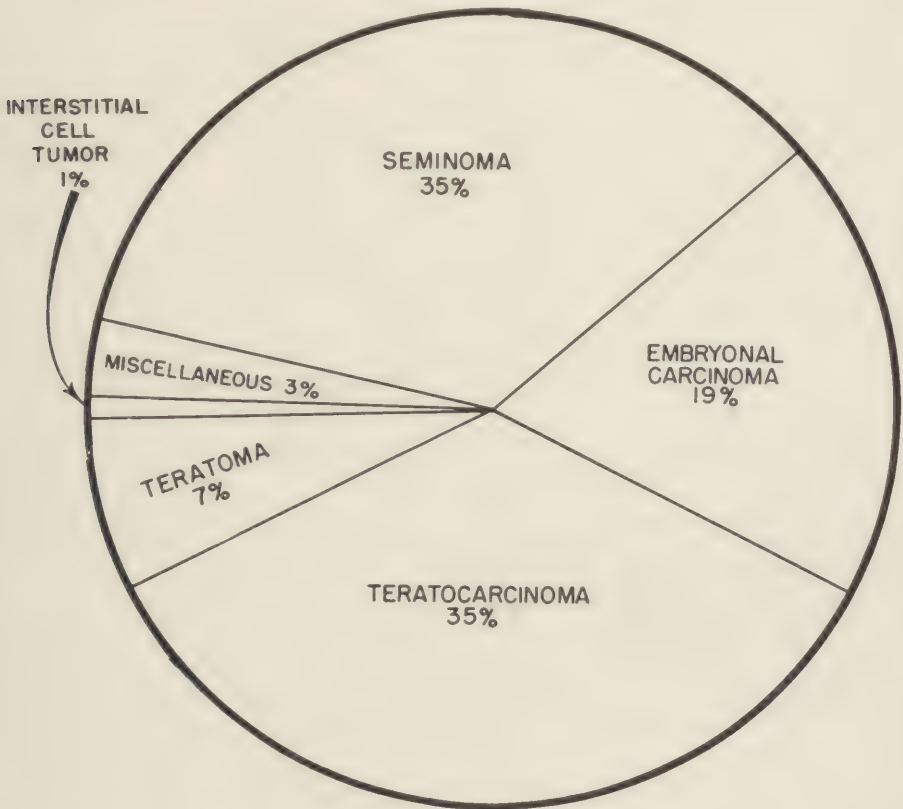


FIG. 1. Percentage distribution of testicular tumors.

tural patterns and the mortality rates. The data were derived from study of 922 tumors of the testis collected at the Army Institute

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The fact that only 4 fundamental structural patterns (seminomatous, embryonal carcinomatous, chorioepitheliomatous and teratomatous) were encountered, alone or in combination, in the vast majority of the tumors permitted use of the following simple classification:

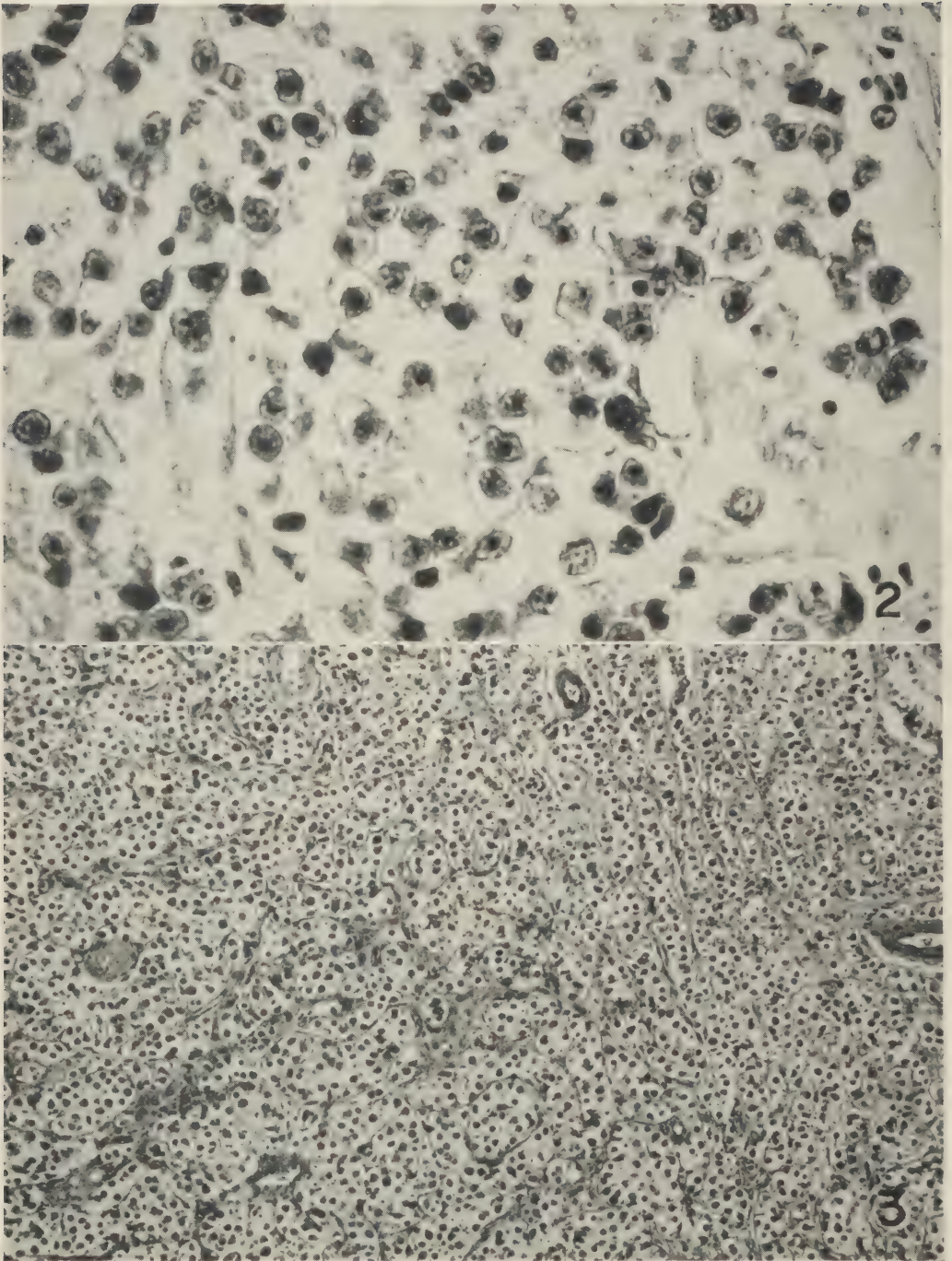


FIG. 2. Seminoma, showing typical clear cytoplasm and sharp borders of cells. $\times 550$.

FIG. 3. Pseudotubular clusters of cells in seminoma without lymphoid stroma. $\times 130$.

1. Seminoma (germinoma)
2. Embryonal carcinoma
 - 2A. Chorioepithelioma
3. Teratoma
4. Teratocarcinoma

Over 96 per cent of the neoplasms fell into one of these categories; of the remainder 1 per cent were interstitial cell tumors, and 3 per cent were rare or unclassifiable varieties. The percentage distribution of the different

types is indicated in Figure 1. Chorioepitheliomas were included with embryonal carcinomas. Seminomatous tissue was present in about 20 per cent of embryonal carcinomas and teratocarcinomas, but the seminomatous components of such neoplasms were ignored in classification because their presence did not affect the behaviour of the tumors.

SEMINOMA

One third of the tumors were monocellular seminomas. They were made up of rounded

cells were usually arranged in unorganized masses of cords divided by trabeculae of connective tissue. Differentiated glandular epithelial structures were almost never produced by seminoma cells, although occasionally cords and columns formed pseudotubular aggregates without lumens (Fig. 3).

Although seminomas comprised a more homogeneous group than any other type, certain variations in structure did occur. In some instances the cytoplasm was darkly stained instead of clear. Rare "anaplastic" seminomas

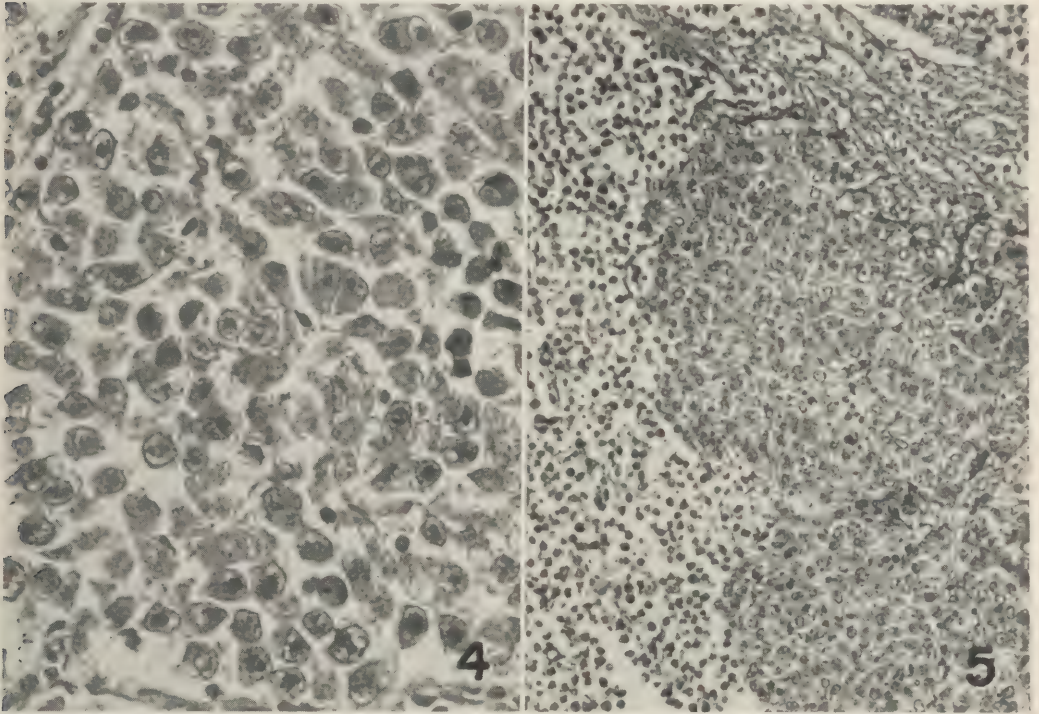


FIG. 4. Anaplastic seminoma. The nuclear pattern resembles that of embryonal carcinoma. $\times 450$.

FIG. 5. Junctional zone between seminomatous and embryonal carcinomatous components of a mixed neoplasm. $\times 130$.

polyhedral elements with sharp cell borders; the cytoplasm was often clear (Fig. 2). The round, centrally placed nuclei were clearly outlined by a membrane, and the nucleolus, which was usually but not invariably single, was also centrally located. The nuclear chromatin, apart from the nucleolar masses, was evenly dispersed; the beading at the interstices of the fine chromatin net imparted a stippled pattern to sections examined under low magnification. The remarkably uniform

offered diagnostic difficulties because their nuclei were hyperchromatic and irregular and bore some resemblance to the pattern seen in embryonal carcinomas (Fig. 4). Such unusual tumors, to which the term "seminoid carcinoma" might be applied, were exceptions to the rule that seminomas and embryonal carcinomas are differentiated with ease. In a few seminomas foci of anaplasia were seen in expanding growth centers.

In about 4 per cent of the 922 tumors both

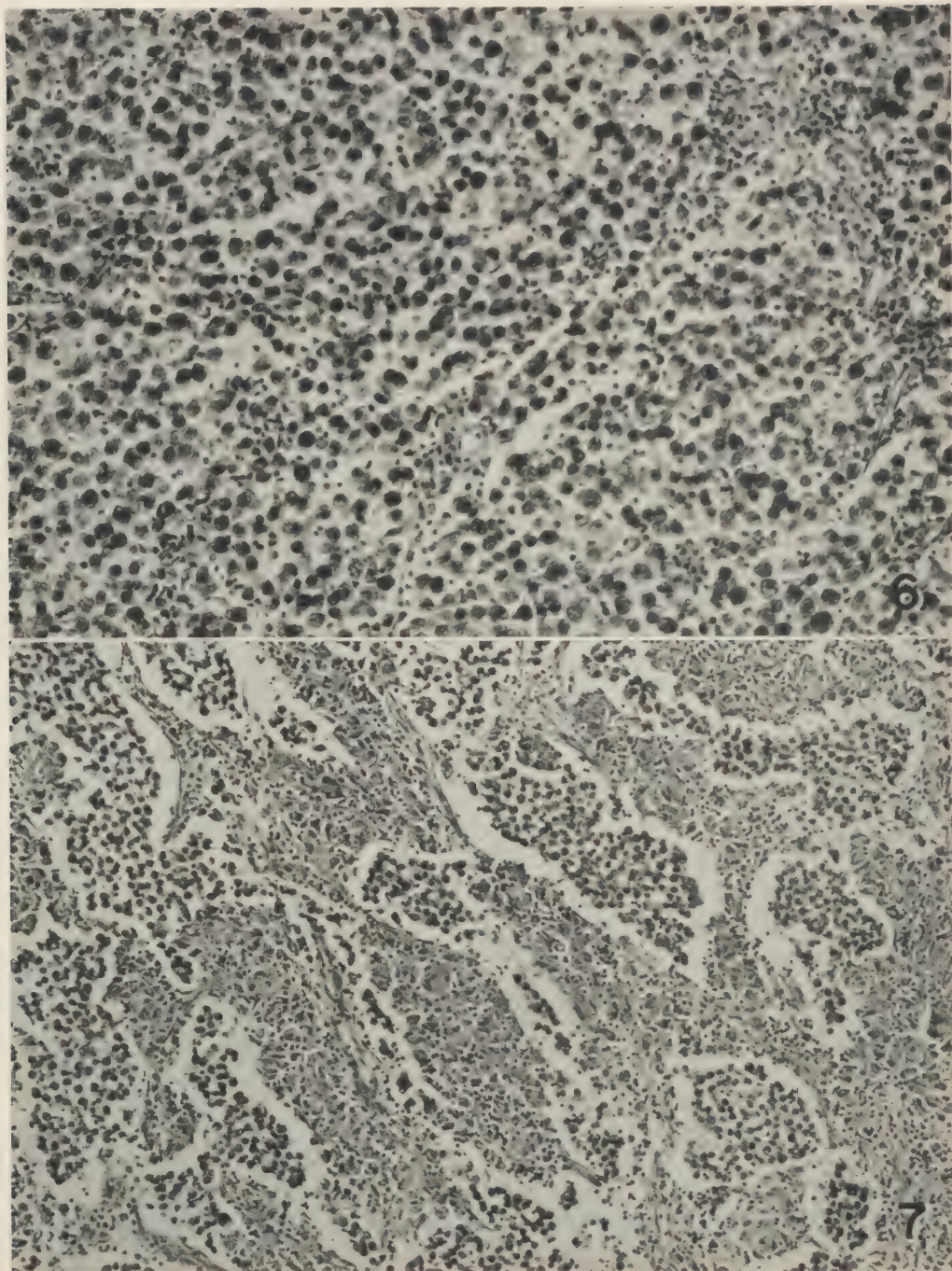


FIG. 6. Seminoma with lymphoid stroma. $\times 230$.

FIG. 7. Seminoma with abundant granulomatous stroma which contains many epithelioid cells. $\times 130$.

seminomatous and embryonal carcinomatous tissue were encountered. All tumors in this group were classified as embryonal carcinomas, regardless of the relative distribution of the

2 types of structure, because the presence of even a small focus of carcinoma greatly worsens the prognosis for the patient. In different tumors the 2 elements were separate

and discrete, contiguous or closely intermingled. When the 2 types were intimately associated the junctional zone usually suggested that the more malignant carcinomatous elements were invading the seminomatous tissue (Fig. 5). In rare instances it seemed as if transitions could be made out and that embryonal carcinoma cells were developing from

encountered in ovarian dysgerminomas, were commonly observed. Sometimes the formation of granulomas (Fig. 7) and fibrosis were so extreme that only scattered neoplastic cells remained; fibrous nodules occasionally formed in this way. Furthermore, not only were many seminomas devoid of lymphoid cells (Fig. 3), but occasional embryonal carcinomas showed

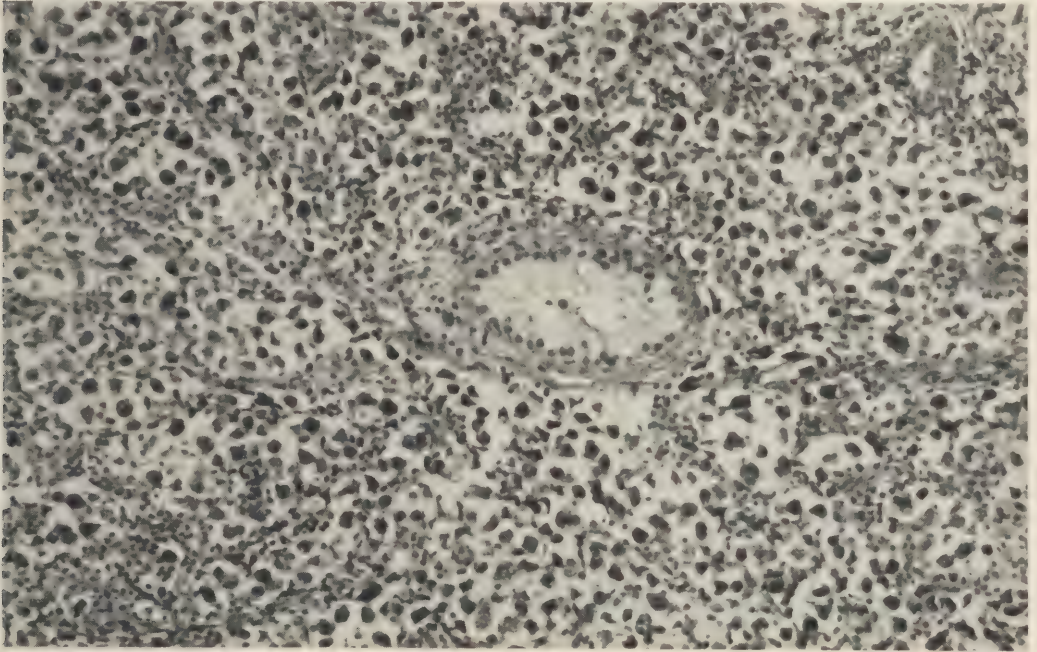


FIG. 8. Atrophic seminiferous tubule entirely surrounded by seminoma cells. $\times 185$.

seminoma cells.

Most of the neoplastic giant cells encountered contained multiple nuclei of the seminoma type, but occasional syncytiotrophoblastic elements were also present. Giant cells of the foreign body and Langhans types were common in the peculiar stroma of many seminomas.

The lymphocytic infiltration of the trabeculae of connective tissue in seminomas (Fig. 6) has led to the use in some laboratories of the designation "embryonal carcinoma with lymphoid stroma." Although cells resembling lymphocytes were certainly the most common type of secondary element, the stroma was often infiltrated with eosinophils and plasma cells. Epithelioid cells and tuberculoid granulomas with giant cells, similar to those

typical "lymphoid stroma." The misleading term "embryonal carcinoma with lymphoid stroma," which designates neither a clinical nor a pathologic entity, was not used in classifying the neoplasms in this series. Most of the tumors to which it could be applied were seminomas; a small minority were true embryonal carcinomas.

Foci of coagulation necrosis were often encountered; the necrotic masses were characteristically bordered by a zone of palisaded macrophages and foam cells. The florid hemorrhagic necrosis of chorioepitheliomas and embryonal carcinomas was not seen in seminomas. As seminomas grow they respect tissue planes and adjacent structures and do not aggressively invade and destroy as do embryonal carcinomas. For example, surviv-

ing testicular tubules (Fig. 8) are often observed within the neoplastic tissue. Invasion of the adnexae and cord is exceptional, while it is the rule for embryonal carcinomas. The small incidence of regional and distant metastasis and the low mortality rate are consistent with the relatively benign appearance of seminomas.

Pure seminomas occurred in relatively older men than did the other types of neoplasms. The incidence of seminomas and teratocarcinomas, comparably common tumors, among men of

with seminomas although these tumors differ not only in fundamental cell type but in biologic behavior and prognosis. The neoplasms designated "embryonal carcinoma" include, among other types, those called "embryonal adenocarcinoma" and "papillary adenocarcinoma." As will be pointed out, even chorioepitheliomas probably belong in this group.

Embryonal carcinomas showed considerably more variation in cellular type from tumor to tumor and in different portions of the same tumor than did seminomas. The cells were

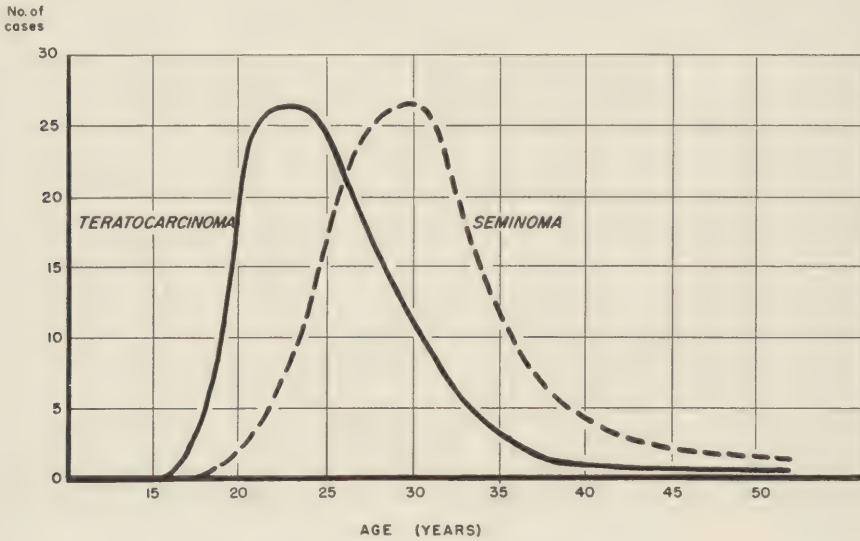


FIG. 9. Frequency distribution of seminomas and teratocarcinomas by age group. Seminomas occur in older men.

various ages is given in Figure 9. It should be pointed out that the difference (5 years) between the two means of 25 and 30 is 25 per cent of the range into which the ages of most of the patients fell. In Figure 10, which presents the same data, account is taken of the number of men in the Army in each age group; it shows that the incidence of teratocarcinoma was roughly the same over the entire range, while that of seminoma continued to rise with age. The downward curve after 45 cannot be properly evaluated because the number of men affected and the total Army population in this group were too small.

EMBRYONAL CARCINOMA

Embryonal carcinomas are often confused

frankly epithelial, often cuboidal or columnar, and frequently formed differentiated glandular or papillary structures. Differentiation was often incomplete, so that portions or all of a tumor consisted of unorganized solid epithelial sheets. The obviously anaplastic cells were larger than those of seminomas (Fig. 11). The nuclei, which were large, variable and bizarre, showed few traces of the orderly seminomatous pattern; the chromatin was clumped irregularly into large masses which stood out sharply against the clear background.

Although embryonal carcinomas can be divided into a number of varieties on morphologic grounds, biologic significance and prognostic import cannot as yet be ascribed to all of them. A few distinctive patterns deserve

comment because of their frequent occurrence. Glandular structures, often strikingly papillary, characterized a common neoplasm (Fig. 12); the cytoplasm was often clear basally, and there was a cuticular or hairy cell border. In other tumors the epithelial cords formed anastomosing trabecular networks; a variant of this picture was seen in the reticular type (Fig. 13), in which the anastomosing epithelial cords intertwined with the stroma, as

solid sheets and masses. Usually the tumors resembled only the cytotrophoblastic components of chorioepitheliomas, but occasionally dark smudgy elongated cells appeared to be applied against the predominant cells (apliquéd), as if an attempt were being made to reproduce the biphasic cytotrophoblastic and syncytiotrophoblastic pattern (Fig. 14). Frank syncytial trophoblastic elements were often present focally (Fig. 15), and fully differen-

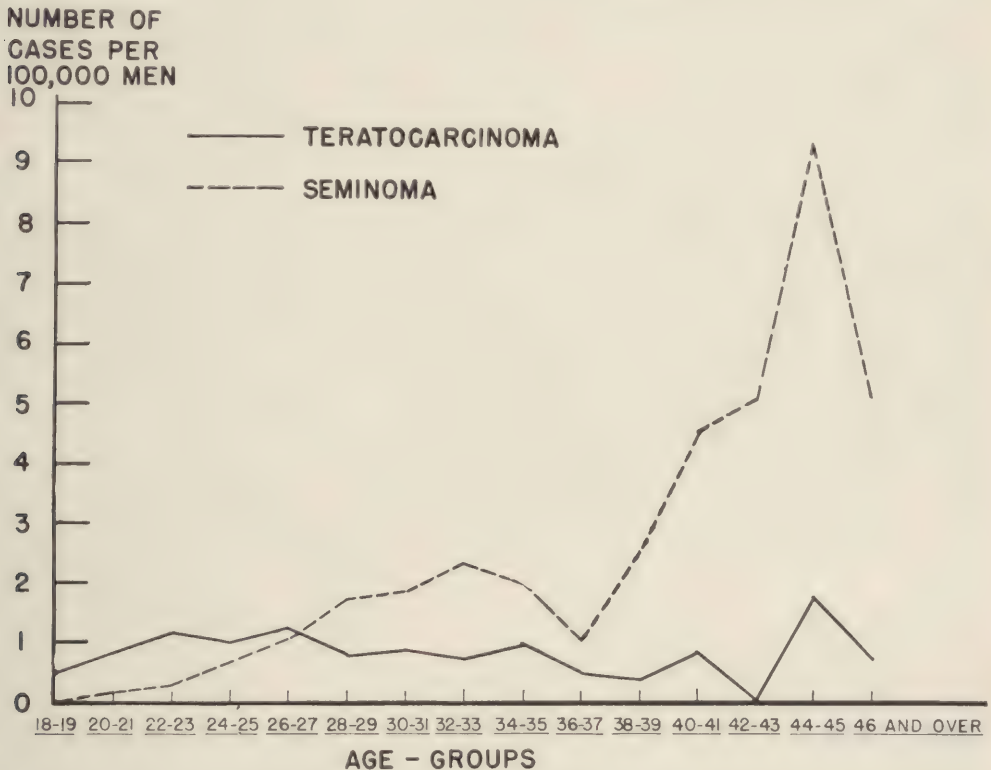


FIG. 10. Incidence of teratocarcinoma and seminoma corrected for Army population in each age group. Incidence of teratocarcinoma is practically constant, while that of seminoma rises with age.

in mixed tumors.

The striking resemblance to trophoblastic tissue of one common variety of embryonal carcinoma warrants special emphasis. The cells of such neoplasms showed prominent masses of chromatin against a clear nucleoplasm. The cytoplasm tended to be clear and granular, as in well glycogenated liver cells. Loss of distinct cell outlines and superimposition of nuclei in syncytial cytoplasmic masses was often seen, particularly in tumors growing chiefly as

tiated chorioepitheliomatous tissue was encountered in about 6 per cent of embryonal carcinomas. The hemorrhagic necrosis of both neoplastic and infiltrated tissue and the vascular invasion which characterize chorioepitheliomas were frequently seen in embryonal carcinomas. Recognition of the trophoblastic nature of many embryonal carcinomas (and the carcinomatous component of teratocarcinomas) makes understandable the occurrence of secondary endocrine changes, such as

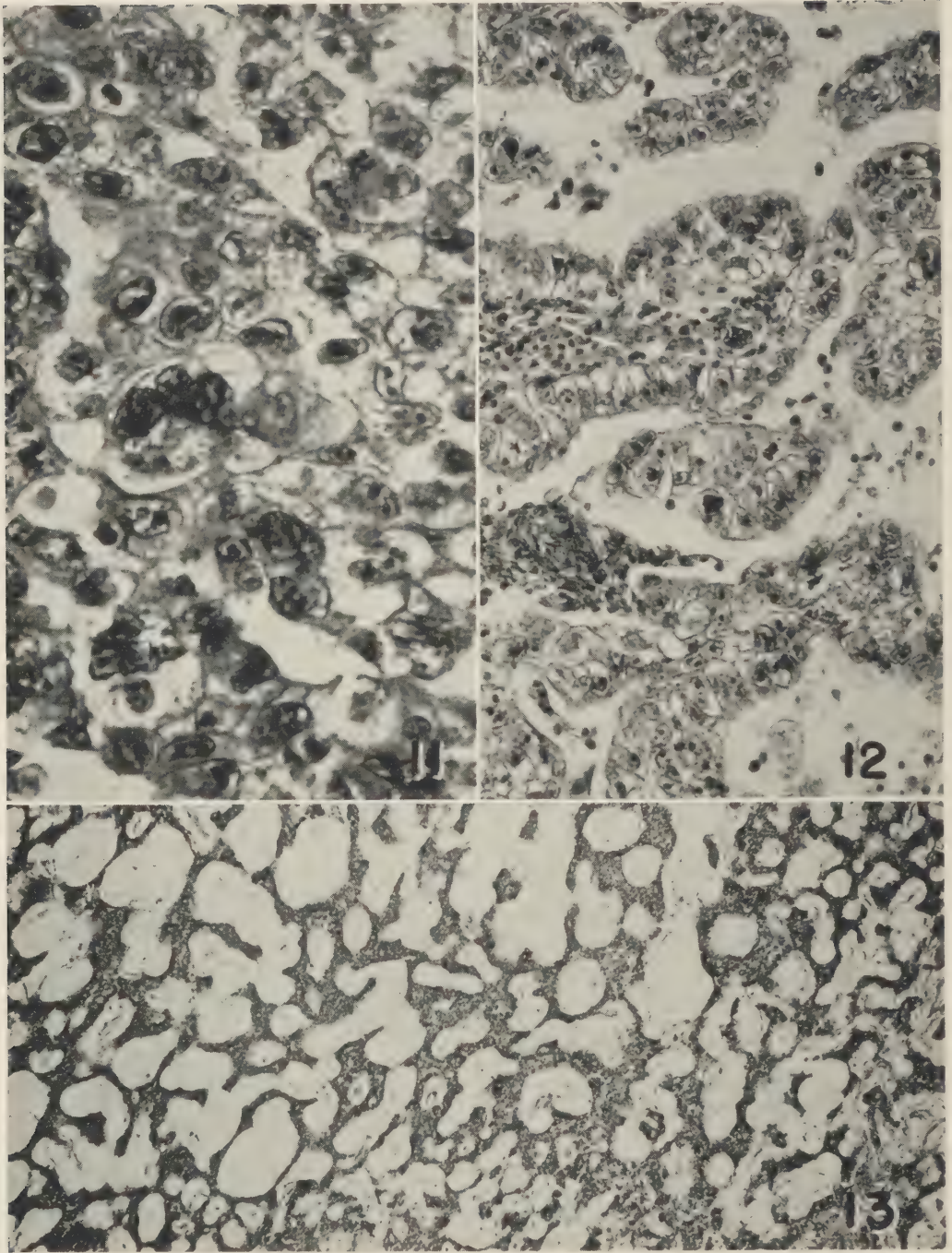


FIG. 11. Embryonal carcinoma. Large irregular hyperchromatic nuclei of the anaplastic cells contrast with the regular pattern of the elements of the seminoma (see Fig. 2). $\times 550$.

FIG. 12. Papillary adenocarcinoma, a variety of embryonal carcinoma. $\times 250$.

FIG. 13. Reticulated type of embryonal carcinoma. $\times 70$.

gynecomastia, in association with tumors of this type.

The differentiation of frankly teratoid

structures within an embryonal carcinoma automatically placed such a neoplasm in the category of teratocarcinoma, but certain pat-

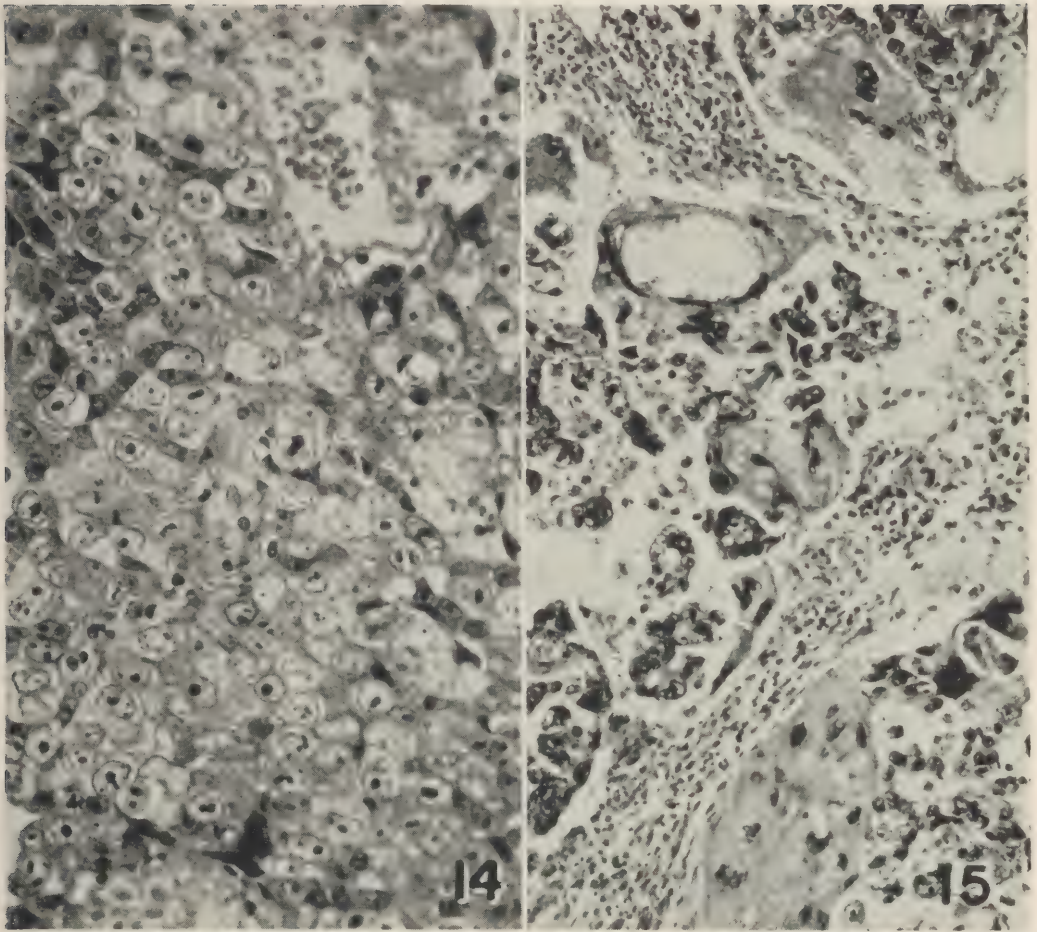


FIG. 14. Trophoblastic embryonal carcinoma. Cells have cytotrophoblastic appearance, and secondary cellular components seem to be appliquéd against predominating elements. $\times 315$.

FIG. 15. Syncytial cells in a trophoblastic embryonal carcinoma. $\times 160$.

terns indicating early or minimal differentiation were recognizable in tumors classified as embryonal carcinomas. For example, condensation of mesenchyme (Fig. 16) around or next to the neoplastic epithelium in some embryonal carcinomas actually represented the beginnings of specialization and differentiation although it could easily be mistaken for an ordinary desmoplastic reaction. In other neoplasms there were microcystic structures (Fig. 17) bordered by regularly arranged cellular rows and arcs with the general conformation of early embryos, other indications of primitive differentiation; sometimes a trophoblastic cushion (Fig. 18) adjoined the embryonic disks.

CHORIOEPITHELIOMA

Chorioepitheliomas have such a characteristic appearance that they are easily recognized under the microscope, and their nature may often be suspected grossly because they are strikingly hemorrhagic. These neoplasms typically have two cellular components, and their arrangement duplicates the architecture of the placental villi. The combination of compactly grouped cytotrophoblastic cells and giant multinucleated syncytial structures, which usually are arranged at the borders of the cellular masses, makes one of the most striking microscopic pictures in all pathology (Fig. 19).

Chorioepitheliomas, partly because of the unusual morphologic appearance of classic

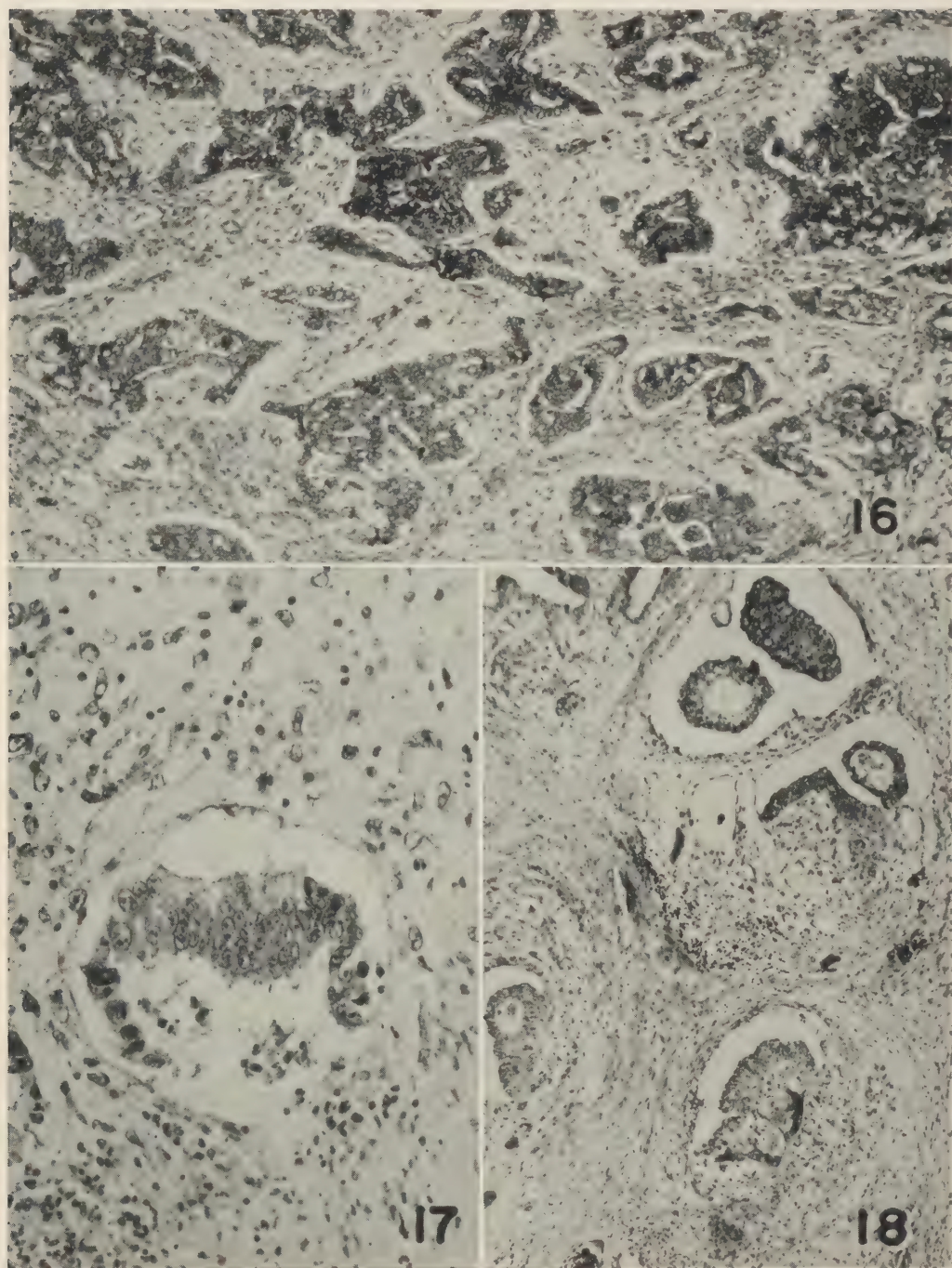


FIG. 16. Condensation of mesenchyme about carcinomatous epithelium in embryonal carcinoma. $\times 110$.

FIG. 17. Embryoid body in embryonal carcinoma. $\times 260$.

FIG. 18. Embryoid body and trophoblastic cushion in embryonal carcinoma. $\times 70$.

examples, have usually been placed in a special category. However, during the course of this study it became apparent that frankly

trophoblastic elements occurred focally in many tumors of other types and that even in the absence of syncytial elements trophoblastic

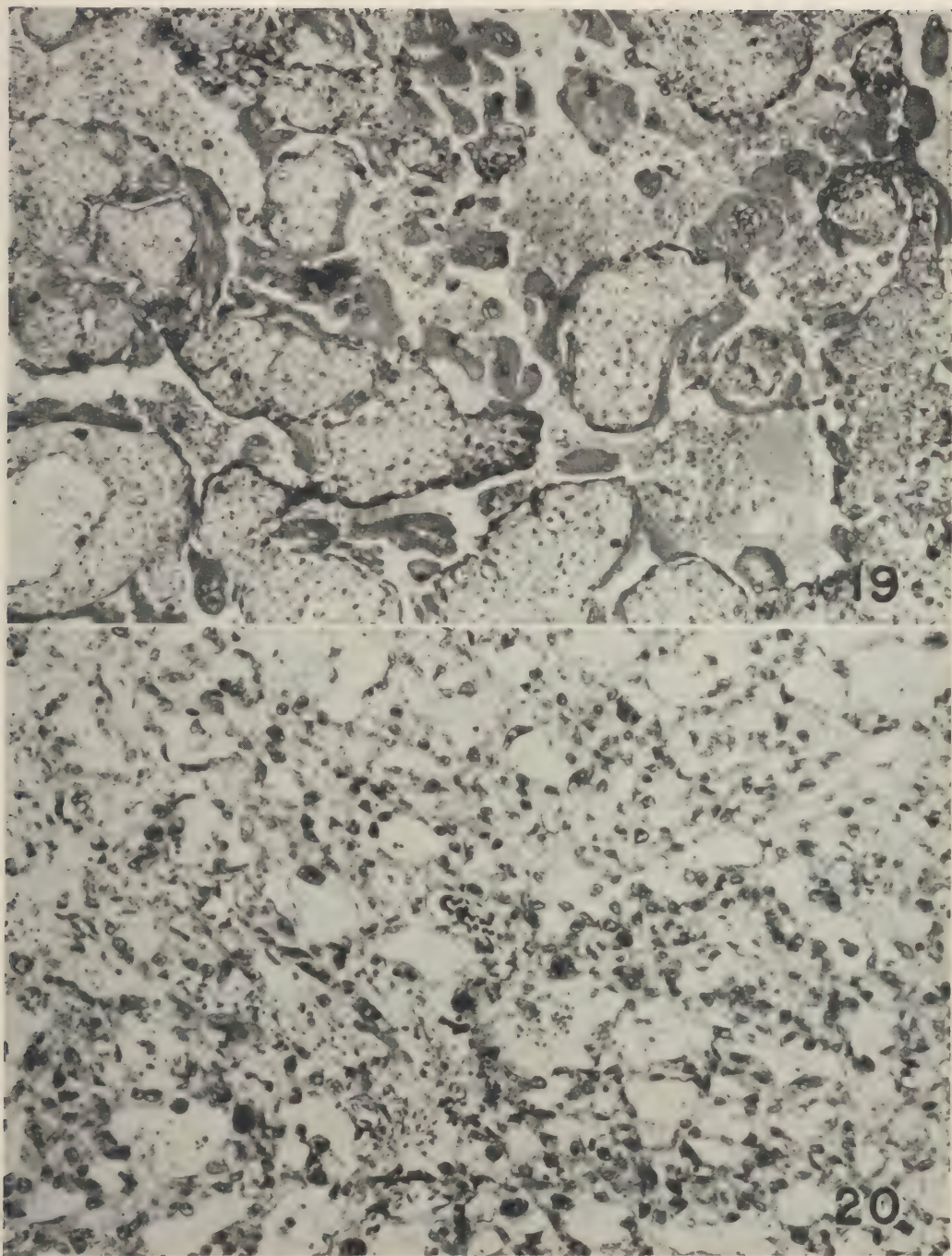


FIG. 19. Chorioepithelioma, showing syncytial cells covering masses of cytotrophoblast. $\times 145$.

FIG. 20. Chorioepithelioma with atypical reticular pattern. $\times 175$.

features were evident in neoplasms usually put in other categories, the embryonal carcinomas in particular. Pure primary chorioepitheliomas comprised only a small proportion of the entire group of testicular tumors (less than 0.4

per cent). Focal chorioepithelioma was rarely observed in seminomas but was encountered in 12 per cent of the embryonal carcinomas and teratocarcinomas (6.4 per cent of the entire series).

Gynecomastia and related changes in the endocrine glands were associated as often with embryonal carcinoma or teratocarcinoma as with chorioepithelioma. The fact that chorionic gonadotropin is often present in the urine of patients with "embryonal adenocarcinoma" provides physiologic substantiation for the morphologic observation that many embryonal carcinomas are trophoblastic tumors.

not setting chorioepitheliomas apart from the embryonal carcinomas, there is no objection to using the designation for tumors clearly of that type.

The trophoblastic potency of embryonic cells is expressed in the chorioepitheliomas and other trophoblastic tumors, while the complementary potency to form somatic structures is expressed in the teratoid tumors.

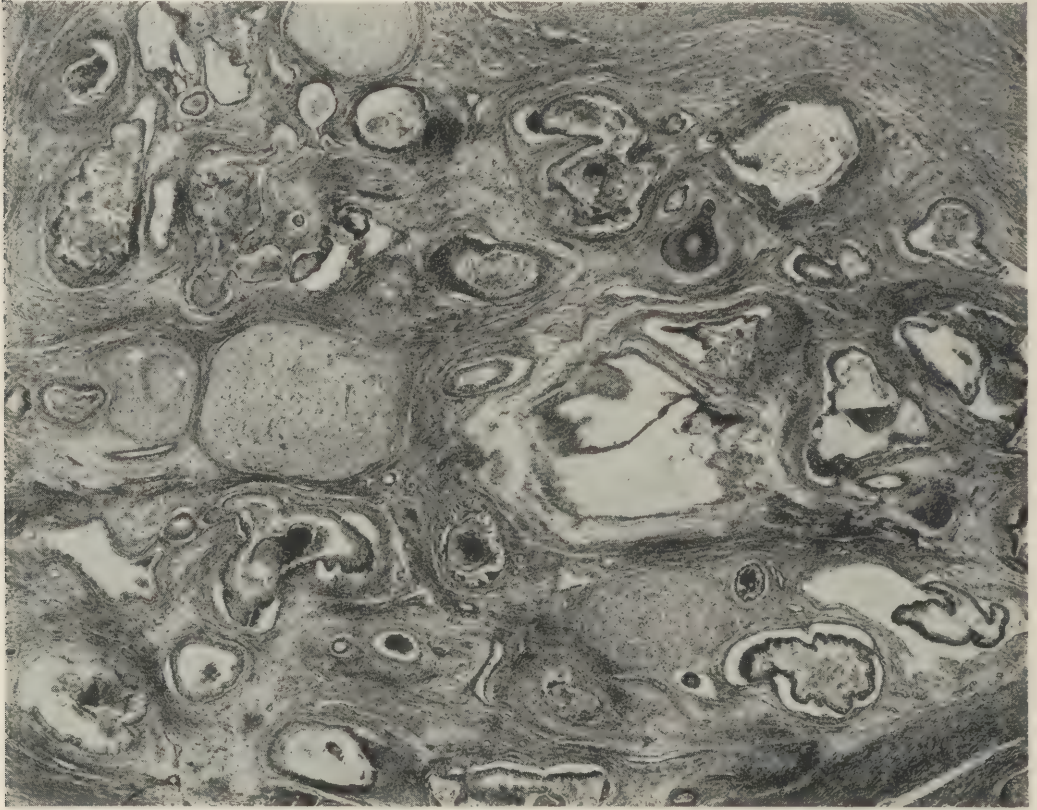


FIG. 21. Teratoma. $\times 8$.

Even unequivocal chorioepitheliomas often differed in appearance from the classic type. For example, the cells were sometimes arranged in a loose reticulum or reticulated syncytium (Fig. 20), with clumps and strands of eosinophilic fibrinoid material in the meshes of the network. Since such patterns were recognized in both embryonal carcinomas and chorioepitheliomas, the concept of chorioepitheliomas as a subvariety of carcinoma rather than as a separate entity is further supported. Despite the practice followed in this study, of

TERATOMA

The teratomas of the testis, with their mad array of ordered and disordered structures, have fascinated pathologists for generations. The range of differentiated structures, both recognizable and unrecognizable, is so great and their admixture so complicated that the completely realized and the partially unfolded patterns are rarely duplicated exactly. If a teratoma has no histologically recognizable malignant components, the qualified designation "adult" is justified; the term "benign"

should never be used, because metastasis of testicular tumors which appeared to be only adult teratomas has occurred.

Teratomas (Fig. 21) are characterized by the presence of epithelial masses, glands and cysts, many of which are organized in combination with undifferentiated or specialized mesenchymal tissues, such as cartilage, into structural units. The components abut on one

rarely encountered. Squamous epithelial nests and cysts, often keratinizing, were frequent, but glandular appendages and adult hair were rare. Epidermoid cysts outnumbered dermoid 10 to 1. Nests of noncornifying epithelium resembling the stomodeal lining were common, and in a few tumors early dental germs were identified; fully formed teeth were never seen.

Masses of neuroepithelium often resembled

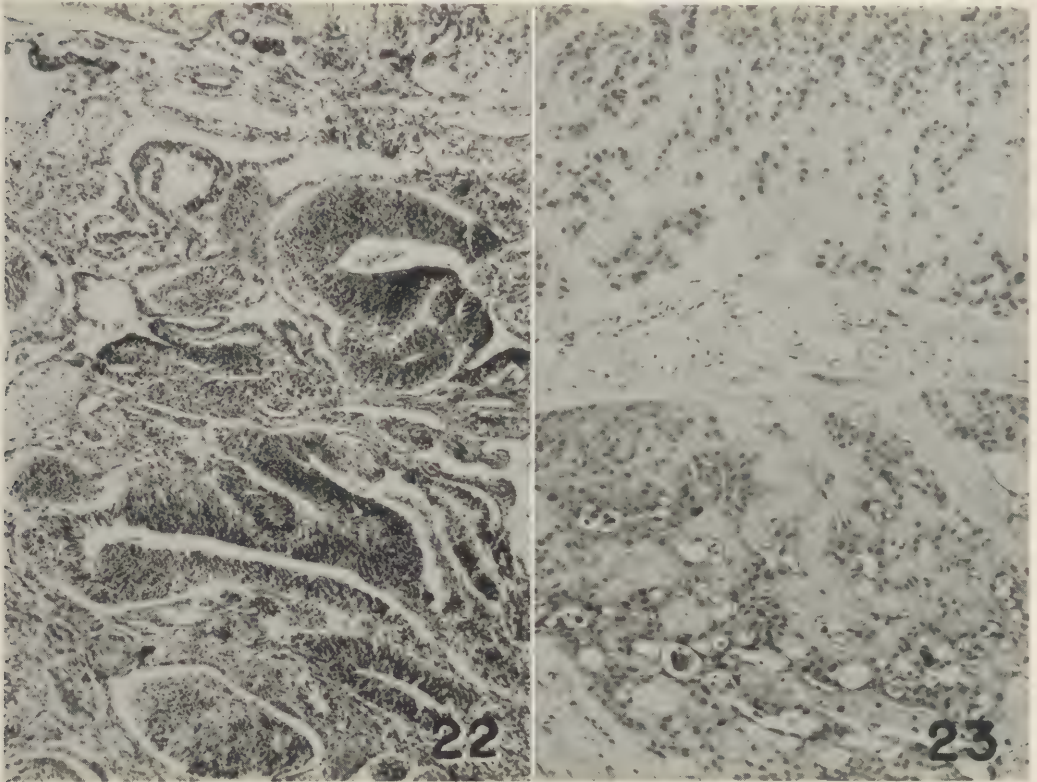


FIG. 22. Masses of neuroepithelium resembling fetal neural tubes in teratoma. $\times 70$.

FIG. 23. Mixed tumor of salivary gland in teratoma. $\times 110$.

another, intermingle, show transitions and generally form a complex of confusing constellations in which, nevertheless, a semblance of organization often can be discerned. Attempts have been made to identify specific architectural patterns as homologues of normal parts of the body, but it is generally admitted that it is easy to force such analogies too far.

Although primitive and undeveloped "primordia" of many kinds were observed, the corresponding highly specialized tissues or differentiated derivatives and their organs were

distorted and complexly fused neural tubes (Fig. 22). Occasionally the proliferation of neuroepithelium resulted in the formation of a neuroblastoma; some neuroblastic metastases occurred. Illy formed glial nests were far more common than the occasional organized bits of neural tissue which included ganglion cells. In a single tumor meninges had formed on the surface of a brain-like mass.

Enteric glands and cysts which were lined by columnar mucinous epithelium and often had organized coats of smooth muscle were

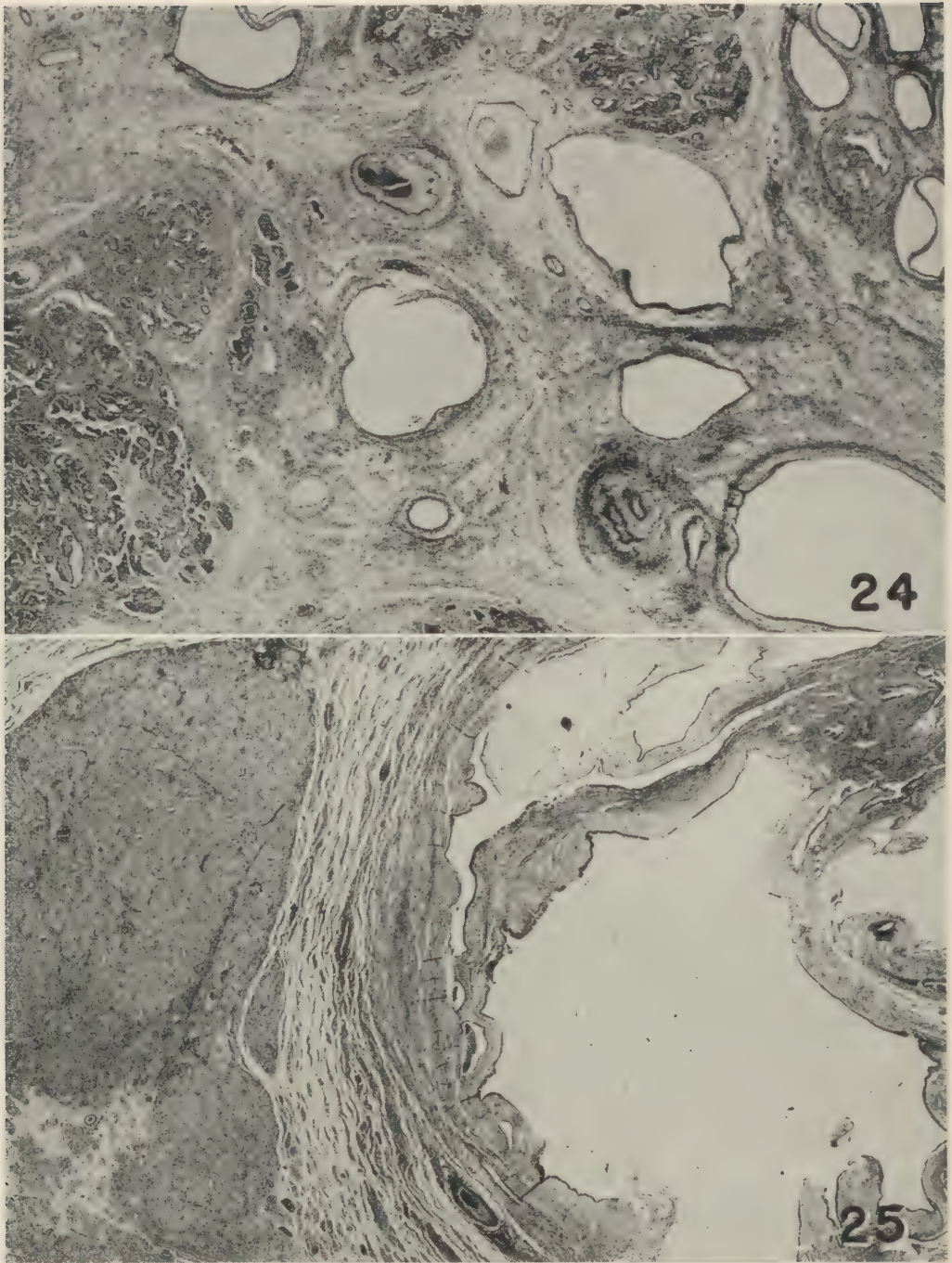


FIG. 24. Teratocarcinoma, showing intermingling of embryonal carcinoma and differentiated teratomatous structures. $\times 15$.

FIG. 25. Teratocarcinoma composed of discrete teratoma and seminoma. $\times 10$.

regularly observed. A few auxiliary glandular structures were recognized, but differentiated secretory elements, such as parietal or zymogenic cells, were almost never present. It is

worth noting that tissue clearly similar to that of mixed tumors of salivary glands (Fig. 23) formed part of one and nearly all of a second neoplasm. In many regions of another tumor

there was a papillary epithelial growth composed of strongly eosinophilic "onkocytes." Frank thyroid or pancreatic tissue was never encountered, nor was liver. Respiratory epithelium was not infrequent; it was sometimes intimately associated with lymphoid tissue and occasionally with cartilaginous arches, but clearly bronchial or pulmonary structures were not identified. Similarly, although transitional epithelium of the urinary type was often found, prostatic acini were seen only once and an

were not observed. An angioendotheliomatous type of proliferation appeared twice.

The term "teratoma" is loosely used in this report to designate any growth in which differentiated "adult" structures were recognized. There appeared to be no reason for distinguishing between solid and cystic teratomas. For convenience, dermoid and epidermoid cysts were included in the group of adult teratomas, of which they made up about 16 per cent.

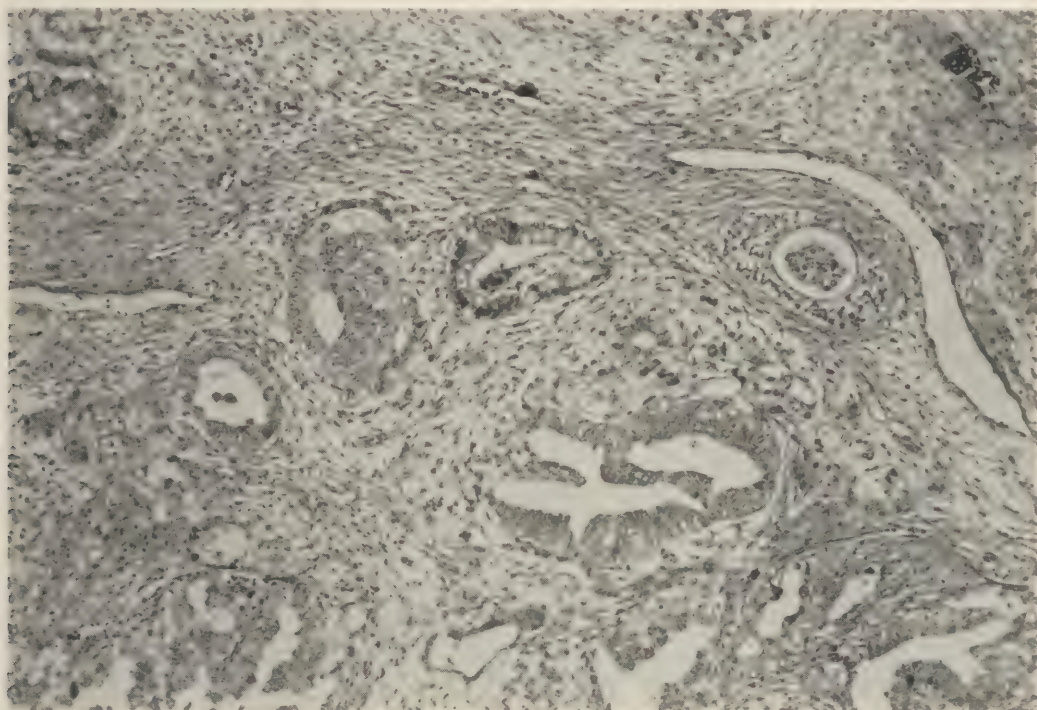


FIG. 26. Teratocarcinoma, showing differentiation of squamous nest and mucinous gland in situ. $\times 60$.

organized structure resembling vesical wall only twice.

Embryonic mesenchyme was commonly organized into special structures surrounding or satellite to epithelial tissue and was often differentiated into smooth muscle and cartilage. Skeletal or cardiac muscle and bone, on the other hand, were only occasionally identified. Mucinous connective tissue and young fat cells, sometimes arranged in lobules, were often present; but adult adipose tissue was rare. Lymphoid tissue was frequently abundant, but hematopoietic tissue or lymph nodes

TERATOCARCINOMA

The frequency with which the monocellular tumors occur in intimate and complicated association with teratomas is partially responsible for the array of complex classifications in the literature. A new term, "teratocarcinoma," is proposed for the large group of pleomorphic tumors in which both differentiated teratoid structures and histologically malignant elements were present (Fig. 24). Most teratocarcinomas (77.5 per cent) were mixtures of teratoma, embryonal carcinoma and/or chorioepithelioma; but 5 per cent were com-

posed of teratoma and seminoma, and 15 per cent had seminomatous, embryonal carcinomatous and/or chorioepitheliomatous components. The remaining 2.5 per cent formed a heterogeneous group which included the unusual combination of teratoma and neuro-

differentiation occurred more often in teratocarcinomas (15 per cent) than in embryonal carcinomas (6 per cent). The formation of somatic and trophoblastic structures was almost exclusively a property of teratocarcinomas and embryonal carcinomas; such differentiation occurred in rare predominantly seminomatous tumors, but the intimate intermingling of teratoid and carcinomatous elements which characterizes most teratocarcinomas was not present.

The results of this study do not support the conventional theory that malignant tumors of the testis usually arise from teratomas but the series did include a few teratoid tumors in which carcinomas, rhabdomyosarcomas or neuroblastomas developed.

TABLE I
MORTALITY RATES AND INCIDENCE OF
METASTASIS OF DIFFERENT TYPES
OF TESTICULAR TUMORS

Type of Tumor	Total no. of Cases	No. of Deaths from Tumor	No. of Living Patients with Metastasis
Embryonal carcinoma	171	47 (27.5%)	26 (15%)
Seminoma	319	8 (2.5%)	20 (6.5%)
Teratocarcinoma	319	55 (17%)	35 (11%)
Teratoma	68	10 (15%)	9 (13%)

epithelioma and the even rarer association of teratoma and sarcoma. The constituents of teratocarcinomas were usually intimately intermingled but occasionally were segregated, particularly when the tumors were made up of teratoma and seminoma (Fig. 25).

The explanation usually advanced for the presence of embryonal carcinoma in teratocarcinomas is that malignant transformation of an "adult" structural component of a teratoma has taken place. If this theory is tenable, one would expect to encounter squamous cell carcinomas and mucinous adenocarcinomas in teratocarcinomas because squamous epithelial nests and enteric glands and cysts are so frequently present in teratomas. Actually, the carcinomatous component was usually a typical monocellular embryonal carcinoma and was almost never of a specialized epithelial type.

The glands and other differentiated epithelial structures in teratocarcinomas were intimately associated with both carcinomatous epithelium and organized mesenchymal components in such a way that they appeared to have differentiated in situ, probably from the carcinomatous cells (Fig. 26).

Focal or disseminated chorioepitheliomatous

MORTALITY RATES AND INCIDENCE
OF METASTASIS

Two important points must be borne in mind in evaluating the significance of the mortality rates and incidence of metastasis. First, no attempt has been made in this report to evaluate the effects of surgical or roentgenologic therapy. Second, follow-up information regarding the presence of metastases and the results of autopsy is limited for the most part to those patients kept under observation or treatment in Army hospitals for several months after orchiectomy. Few patients were followed up for more than a year. Most of the men were transferred to the charge of the Veterans Administration or to civilian medical care, and comprehensive data from these sources have not yet been compiled.

Evidence of metastasis, such as palpable abdominal masses or roentgenologically demonstrable pulmonary nodules, often established by histologic examination, was obtained in about 10 per cent of the cases; 13 per cent have terminated fatally. Regardless of what the long-term results may prove to be, certain conclusions regarding the *immediate* prognosis for the different types of tumor are inescapable. The number of cases in which autopsy was performed and metastasis occurred is given in table I.

The disparity between the figures for

seminomas and embryonal carcinomas is consistent with the differences in histologic behavior of the 2 tumors. The carcinomas infiltrated adjacent tissues and adnexal structures aggressively and showed hemorrhage, necrosis and vascular invasion. They were of the same order of malignancy as chorioepitheliomas. The relatively benign microscopic appearance of seminomas has already been mentioned. The difference in the relation of mortality rate to incidence of metastasis for seminomas (1:2.5) and for embryonal carcinomas (2:1) indicates that seminomas disseminated more slowly. Metastasis of seminomas was usually restricted to the retroperitoneal tissues or the peritoneal linings; distant or parenchymal metastases were rare, while they were the rule for embryonal carcinomas. The mortality rates and incidence of metastasis for teratocarcinomas were not as high as for embryonal carcinomas but were much higher than for seminomas. It is of exceptional interest that the death rate and incidence of metastasis were practically the same for adult teratomas as for teratocarcinomas.

There are several possible interpretations of the malignant behavior of the "benign" adult teratoma. First, it is possible that the testicular neoplasm was only one of several teratoid tumors which developed multicentrically along the course of the genitourinary tract and that the truly primary malignant neoplasm was extragenital. Secondly, it is conceivable that adult differentiated teratoid tissue had invaded blood vessels and metastasized as such. A third and frequently advanced explanation is that malignant foci in the primary tumor were overlooked, especially if its size was incompatible with study by serial section. However, malignant foci were found in no metastasizing adult teratomas of this series despite careful study by the multiple block technic, which consists of sectioning and embedding of the entire tumor and examination of slides from each block. The fourth, and most satisfactory, theory is that a teratocarcinoma matured into an adult teratoma after malignant embryonal cells had already been disseminated to other parts of the body. The similarities in the struc-

ture of the metastases of teratomas and teratocarcinomas and the natural history of differentiating and evolving teratocarcinomas are consistent with the suggestion that adult teratomas represent matured teratocarcinomas.

STRUCTURE OF METASTASES

Comparison of the histologic compositions of the primary tumor and the metastases yielded considerable information regarding the potencies of the various cell types and the dynamic balance between undifferentiated elements and teratoid structures. Ninety per cent

TABLE 2
NUMBER OF METASTASES OF TESTICULAR TUMORS
SHOWING CHORIOEPITHELIOMA

Primary Tumor	<i>Metastases</i>		
	Pure Chorio- epi- thelioma	Focal Chorio- epi- thelioma	No Chorio- epi- thelioma
Pure chorioepithelioma	4	0	0
Focal chorioepithelioma	5	4	4
No chorioepithelioma	11	11	0

of the embryonal carcinomas metastasized as embryonal carcinomas or chorioepitheliomas; teratoid structures were rare. Forty per cent of the metastases of teratocarcinomas consisted of embryonal carcinomas or chorioepitheliomas, and in 60 per cent there were frank teratoid structures. Half of the secondary deposits of adult teratomas were of the monocellular variety, and half were teratoid.

All degrees of differentiation from slight condensation (Fig. 27) and "specialization" of the stroma about neoplastic epithelium to complex teratomatous structures (Fig. 28) were encountered. The appearance of muscle (Fig. 29) or cartilage (Fig. 30) in condensed mesenchyme and the development of specialized glands within a mass of undifferentiated carcinomatous tissue supported the concept of differentiation *in situ* rather than the idea that a complex teratoid clump of tissue had embolized and then grown.

In addition to the "unfolding" of teratoid potentialities the metastases of embryonal car-

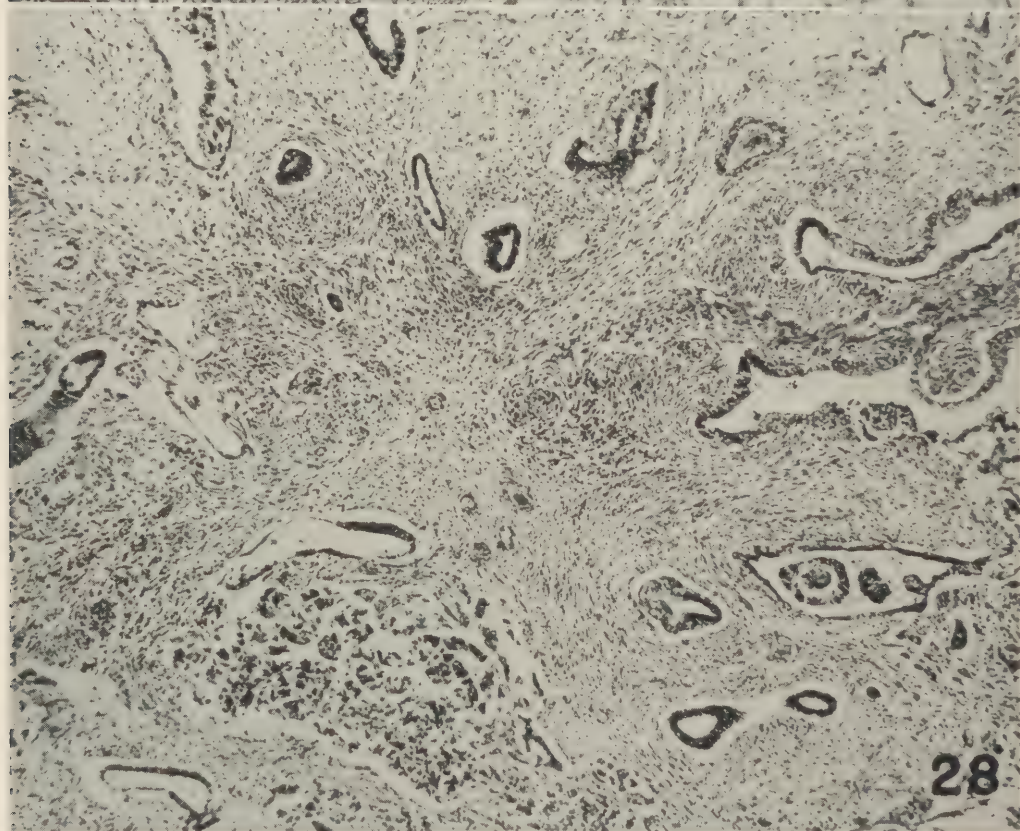
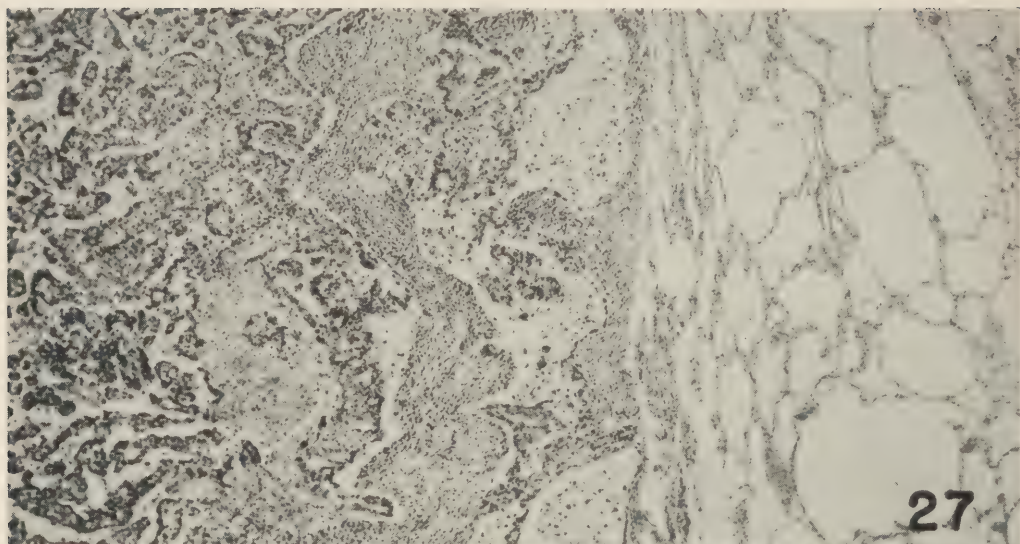


FIG. 27. Pulmonary metastasis of teratocarcinoma showing condensation of mesenchymal elements about neoplastic epithelium. $\times 70$.

FIG. 28. Complex teratoid metastasis in intermediate stage of differentiation. $\times 85$.

cinomas, teratocarcinomas and teratomas may display a complementary development of chorioepitheliomatous tissue. Table 2 shows

that nearly twice as many of the metastases which exhibited chorioepitheliomatous structures arose from primary tumors containing

no chorioepithelioma as from pure chorioepitheliomas or neoplasms containing focal chorioepithelioma. Moreover, metastases of only 4 chorioepitheliomatous primary tumors failed to manifest chorioepitheliomatous structures.

While only 0.4 per cent of the primary

short time thus far, it is reasonable to assume that only the most malignant type of neoplasm will already have caused death and that the number of deaths attributable to this variety of tumor will decrease with the lapse of time. Experience supports this assumption. A survey completed 4 months before preparation of this

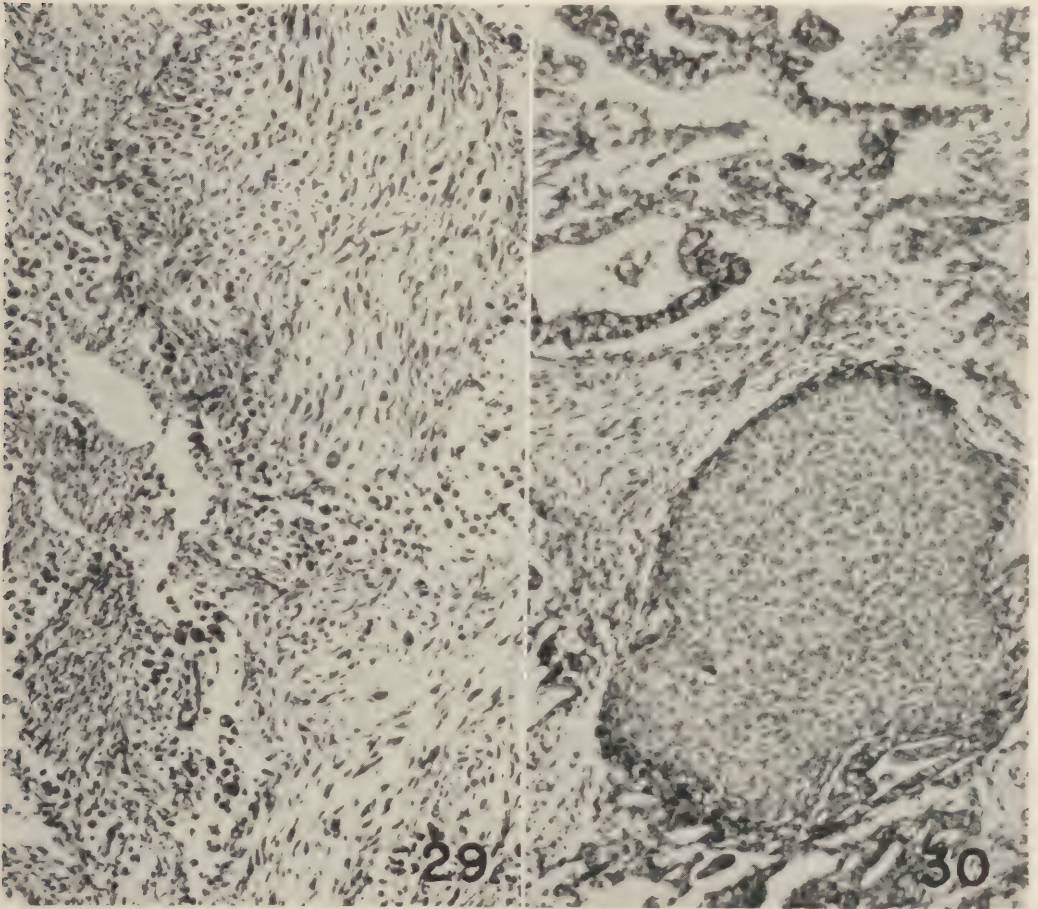


FIG. 29. Muscle fibers in specialized mesenchyme of teratocarcinomatous metastasis. $\times 130$.

FIG. 30. Cartilage in specialized mesenchyme of teratocarcinomatous metastasis. $\times 160$.

testicular tumors were pure chorioepitheliomas and only 6.4 per cent showed focal chorioepitheliomatous tissue, 27 per cent of all the metastases in cases which terminated fatally contained chorioepitheliomatous elements. These figures indicate not only the trophoblastic potencies of the teratoid and carcinomatous tumors but the high degree of malignancy of chorioepitheliomas. Since the patients have been followed up a relatively

report disclosed that 34 per cent of the metastases in cases terminating fatally exhibited either pure or focal chorioepithelioma as contrasted with the current figure of 27 per cent.

Too few patients with seminoma have come to autopsy for conclusions to be drawn regarding the significance of the different types of metastases. Most of the secondary growths studied were in resected retro-

peritoneal nodes; they were largely seminomatous, but a few showed embryonal carcinoma or teratocarcinoma. Seminomatous tissue was rarely encountered in the metastases of those teratocarcinomas and embryonal carcinomas which were associated with seminomas.

In general, the metastases in a given case were uniform, though they occasionally displayed varying structures. For example, some teratocarcinomas metastasized as teratocar-

tissue is present in some mixed neoplasms (see dotted lines in figure 31). They occur in relatively older men and run a relatively more benign course than do the embryonal carcinomas and teratoid tumors. The observation that 80 per cent of the neoplasms in undescended testes encountered in this series were seminomas underlines their biologic individuality and gives rise to interesting speculations regarding their genesis.

The resemblance between seminoma cells

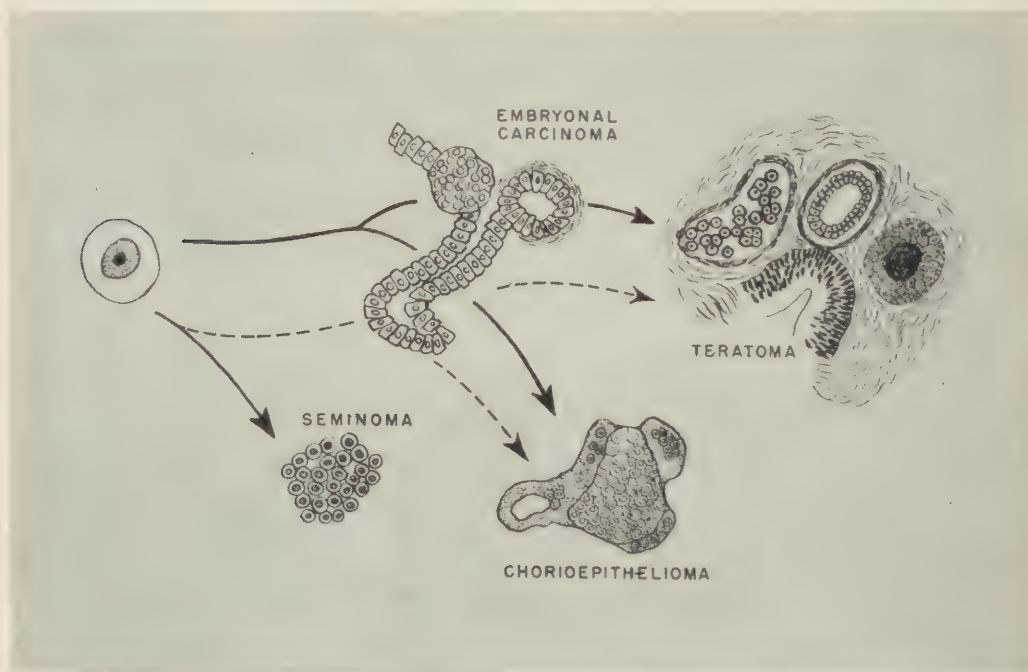


FIG. 31. Schematic presentation of lines of development of testicular tumors.

cinomas to one organ and as embryonal carcinomas or chorioepitheliomas to others. Some differentiated teratoid metastases also contained trophoblastic tissue or isolated syncytial cells. In other words, the metastases, like the primary testicular tumors, showed 4 basic neoplastic patterns which occurred singly or in combination.

MORPHOGENESIS

Seminomas are distinct biologic entities which, for the most part, are pure monocellular growths devoid of teratoid structures in all stages of development, although seminomatous

and some of the elements in seminiferous tubules has been taken as evidence that seminomas arise from the cells (spermatogonia) of the testicular tubules themselves. Although the appearance of tubules invaded and partially replaced by neoplastic cells often gave such an impression, careful comparison revealed that the similarity between neoplastic seminoma cells and spermatogonia was more superficial than real and that the apparent formation of tubular structures was equally illusory. Serial sections of a few small seminomas in an early stage of development, found incidentally in the hilus of the testicle

at autopsy, yielded no evidence supporting the theory of tubular origin. The term seminoma is therefore inappropriate, but it has the advantage of common usage. The designation "disgerminoma," which is employed for the identical tumor occurring in the ovary, or "germinoma" would be more satisfactory than "seminoma." The possibility should be investigated that such tumors represent neoplasms of the so-called primordial germ cells.

The cell of origin of embryonal carcinomas and teratoid tumors has the capacity to form both somatic and trophoblastic tissues, as might be expected of a primitive embryonic cell. The lines along which these neoplasms evolve are indicated in figure 31. Differentiation and specialization may take place focally within the primary growth or may be manifest only in the metastases. The primary and secondary tumors may evolve in different directions; for example, one may form teratoid tissue while the other displays trophoblastic tendencies. Embryonal carcinomas and teratocarcinomas are dynamic, not static; appreciation of the fact that their structural components keep changing and evolving along the lines indicated in figure 31 makes it possible to explain the complex intermingled patterns of some neoplasms. The frequency with which careful study discloses teratoid foci in new growths in the male gonad is understandable in view of the latent potentialities of the neoplastic cells, but it does not mean that all tumors of the testicle arise from teratomas.

The new growths of the male gonad appear exceptional in that they do not reproduce testicular tissue (unless the theory of the tubular nature of seminomas is accepted), while most other neoplasms reflect the architecture of the tissue in which they originate. They express, in distorted fashion, the latent unlimited potencies of the embryonic germ cells from which they arise, while other tumors can make manifest only the limited potencies of their somatic cells of origin. It is important to determine whether a common oncologic principle underlies all new growths or whether

the testicular neoplasms (and other teratoid growths) are truly unique.

SUMMARY

Study of 922 tumors of the testis established that 96 per cent of such new growths can be classified as seminoma, embryonal carcinoma, teratoma or teratocarcinoma.

Seminomas and embryonal carcinomas are distinct tumors which differ not only in fundamental cell type but in biologic behavior and prognosis. Chorioepitheliomas are considered a subvariety of embryonal carcinomas. The term teratocarcinoma is applied to those tumors which show both differentiated teratoid structures and malignant elements and are thought to result from teratoid differentiation in embryonal carcinomas. Monocellular testicular neoplasms do not ordinarily originate from preexisting teratomas.

Virtually all embryonal carcinomas metastasize as monocellular embryonal carcinomas, but choriomatous characteristics may be evident in the metastases of embryonal carcinomas or teratocarcinomas even when they are not manifest in the primary tumor. Roughly half of the teratoid neoplasms which metastasize give rise to growths with teratocarcinomatous structures and half to pure embryonal carcinomas.

Immediate prognosis is bad for embryonal carcinomas and chorioepitheliomas and poor for teratocarcinomas and adult teratomas, which should be regarded as matured teratocarcinomas. Seminomas, in comparison with the other testicular tumors, have a good immediate prognosis.

The architecture of testicular tissue is not reproduced in seminomas, and the neoplastic cells do not resemble spermatogonia. Seminomas are probably tumors of primordial germ cells and should be called germinomas. Embryonal carcinomas and teratoid tumors, which are composed of evolving and differentiating somatic and trophoblastic tissues, are neoplastic expressions of the unlimited potencies of embryonic cells.

PRIMARY INTRACRANIAL NEOPLASMS IN MILITARY AGE GROUP—WORLD WAR II

By MAJOR WARREN A. BENNETT, *Medical Corps*

(With one hundred and six illustrations)

INTRODUCTION

THE great amount of pathologic material sent to the Army Institute of Pathology during World War II has afforded the unusual opportunity of studying a series of intracranial neoplasms in a selected group, namely in Army personnel, between the ages of 18 and 38 inclusive.

Because the statistics presented in this paper have been gathered in so relatively short a period and from a sharply delimited age group, correlations with previous reports cannot be made, but comparisons with statistics from series studied by other authors may be of interest.

A majority of the tumors in this series occurred in persons examined and declared to be in good health upon entering the Army. No history of signs or symptoms of intracranial neoplasm was obtained at the initial examination; relevant symptoms were recorded in only a few cases. It is safe to say that most of the symptoms became evident during the relatively short period in which the person was in active service.

Although intracranial neoplasms in persons over 38 years of age have not been included in the present study, when a significant number appears in any category in the older group they are briefly mentioned.

The material was sent to the Army Institute of Pathology from hospitals and stations all over the world. The study of gross specimens was necessarily limited, because in some instances only blocks of tissue were submitted. The microscopic examination was carried out by the officers in the Section on Neuropathology of the Army Institute of Pathology and only cases with verified diagnoses are included in this series. The clinical records which accompanied the specimens were, on the whole, excellent; some, however, lacked certain data desired for our study.

The primary purpose of this paper is to present the available information on intracranial neoplasms in the military age group. It is in no sense a definitive clinicopathologic study; but rather a survey to indicate the extent of the data and material which has accumulated at the Army Institute of Pathology during the War, and which is available for detailed study of the problems of neuroectodermal and other intracranial neoplasms.

The divisions of this series are based on a morphologic classification as well as on pathogenesis. Only primary intracranial neoplasms have been included; all aneurysms, granulomas, cranial lesions involving the brain, and metastatic intracranial tumors have been omitted, as well as those of spinal cord and peripheral nerves. Reference will be made to the classifications of Cushing;⁷ Baker;⁴ Bailey;² and Elvidge, Penfield and Cone,⁹ for purposes of comparison. We have adopted Cushing's classification for our study, since it is the one most generally accepted.

Globus and Kuhlenbeck^{10, 11} have presented a variant classification to which frequent reference is made in this paper. Their classification is based on the histogenesis of the neuroectodermal elements derived from the medullary epithelium and the differentiation along two main lines, the spongioblastic and the neuroblastic. The derivation of bipotential mother cells from the medullary epithelium is also assumed. These cells, often called medulloblasts, may differentiate into either neuroblasts or spongioblasts. "It is the degree of maturity of these elements and their evolution into the several glial or neuronal cell forms in a varying relative ratio which determine the morphologic character and other biologic features of a given tumor of neuroectodermal origin." A comparative analysis of Cushing's terminology and that of Globus, Kuhlenbeck and others clarifies the points of agreement and divergence.

<i>Cushing, Bailey, and Others</i>	<i>Globus, Kahlenbeck, and Others</i>
Glioblastoma multiforme	Spongioblastoma multiforme
Astrocytoma	Glioma
Astroblastoma	Transitional glioma
Ependymblastoma	Spongioblastoma ependymale
Ependymoma	Ependymoma cellulare Papilloma ependymale Papilloma chorioideum
Oligodendroglioma	Oligodendroglioma
Ganglioneuroma	Spongioneuroblastoma
Ganglioglioma	Transitional glioneuroma Glioneuroma
Spongioblastoma polare	Spongioblastoma polare
Pinealoma	Pinealoma

In the period from Pearl Harbor to V-J Day material from 84,615 cases was received at the Army Institute of Pathology; 543 intracranial tumors made up 0.64 per cent of this total. Ninety-seven of the 543 were not included because the age of the patient was under 18 or over 38, or because the information was inadequate. Thus 446 primary intracranial neoplasms have been studied. Three hundred and eighty-one of these were classified as gliomas (See Table 1, p. 647).

GLIOMAS

Glioblastoma Multiforme: One hundred and two intracranial neoplasms classified as glioblastoma multiforme were found in the series of 446 from the military age group. There was a total of 134 when there was no limitation of age. It will be seen that glioblastoma multiforme represented 22.9 per cent of all tumors in this series and 36.6 per cent of the gliomas. Ninety-nine of these tumors were in males; 93 were in white patients, 8 in Negroes, and 1 in an Okinawan. The ages of the patients averaged 27.6 years.

Glioblastoma multiforme is a soft, gray-red, hemorrhagic, necrotic tumor, usually containing numerous small degenerative cysts. It is very vascular with ill-defined borders. The surrounding brain is gray, glistening, gelat-

inous, and usually of increased consistency. The cut surface varies from gray-pink to bright red due to the degree and age of the hemorrhage and to the amount of necrosis. There is no definite capsule, but the edematous brain about the tumor provides an indefinite line of demarcation. The cortex is invaded causing distortion of the brain (Fig. 1-4).

As the name implies this tumor assumes cellular patterns which are variants of the same process. The morphologic characteristics are: (1) pleomorphism of cells, (2) areas of necrosis and hemorrhage, (3) endothelial proliferation of vessels (Fig. 5 and 6), (4) giant cells, and (5) frequent palisading around areas of necrosis.

Depending on the amount and character of the cytoplasm, the component cells may resemble astrocytes, unipolar and bipolar spongioblasts, and neuroblasts. The nuclei vary in size, shape, and chromatin content. Giant cells with single or multiple nuclei are characteristic of the tumor. The pleomorphic cells do not usually have a particular type of arrangement although around areas of necrosis they tend to assume a palisade pattern. One must remember that various fields in these tumors may show different arrangements and cells; thus areas of small astrocyte-like cells may adjoin others containing numerous neuroblastic elements with many multinucleated giant cells. The pleomorphic cells may be round, fusiform, or piriform. They do not form reticulum or connective tissue (Fig. 7). The cytoplasm is scanty and may appear to surround an almost naked nucleus or to form long processes. The nuclei are said to divide both by mitosis and amitosis. Mitotic figures are common and many are seen to be atypical. The giant cells have numerous nuclei and granular cytoplasm (Fig. 8). Spongioblasts and astrocytes represent the two cells of origin of these giant cells. The perivascular strands of connective tissue are prominent and persist after necrosis.

One of the most characteristic features of glioblastoma multiforme is vascular proliferation. An actual increase in the number of

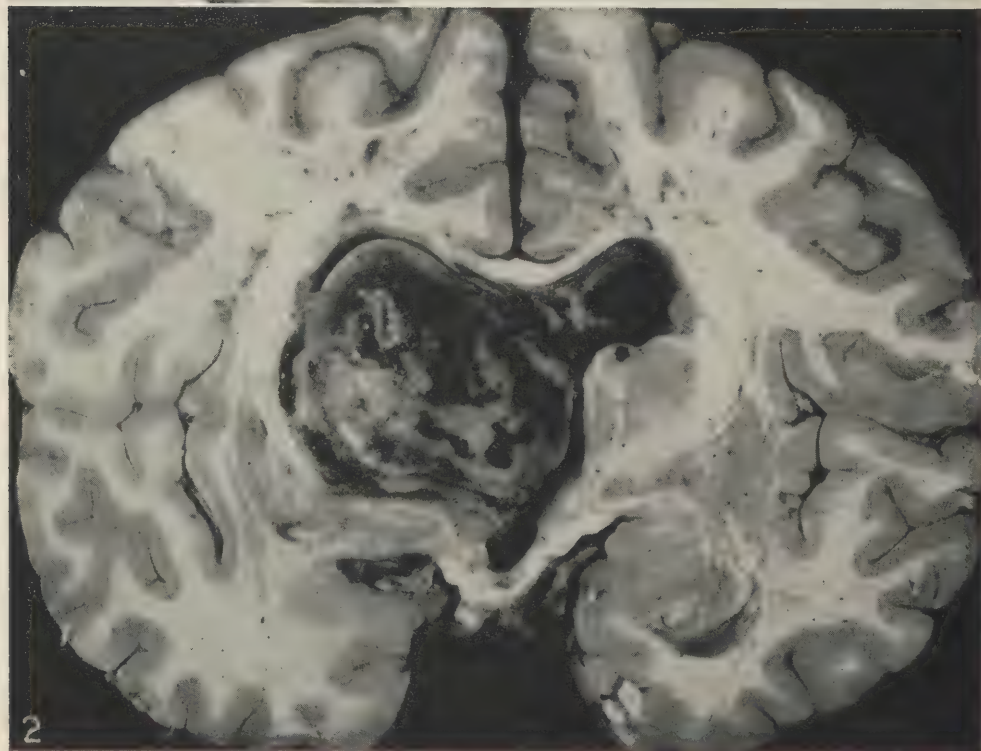
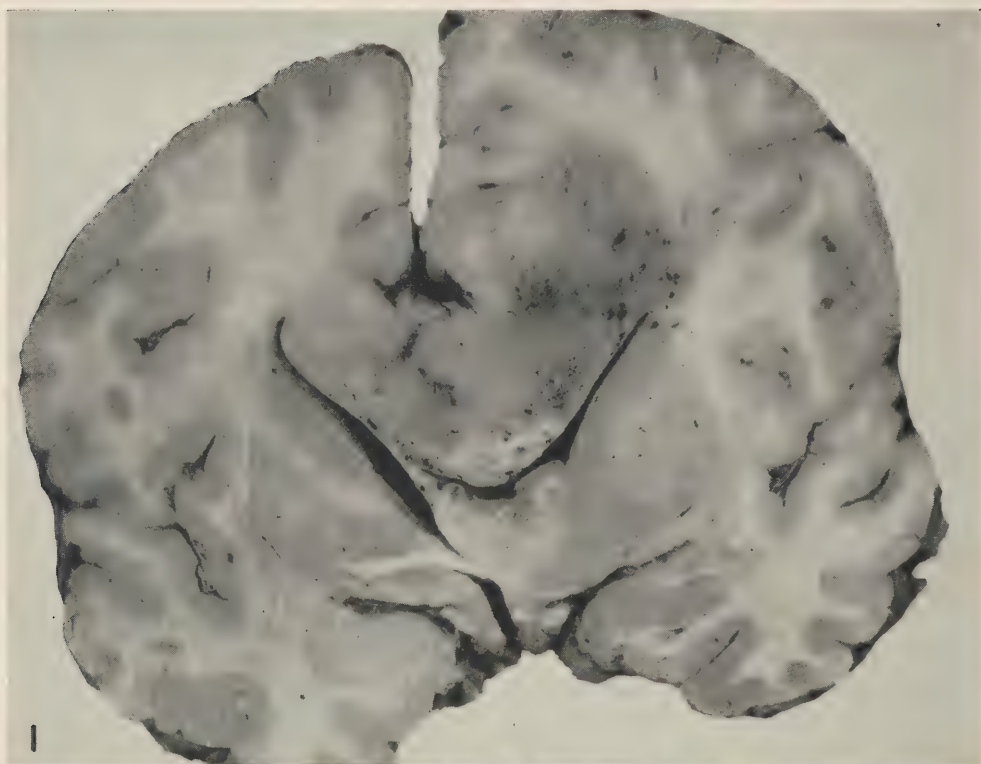


FIG. 1. Glioblastoma multiforme extending across the midline within the corpus callosum. AIP Neg. 78764.

FIG. 2. Glioblastoma multiforme projecting into the lateral ventricle. Note the necrosis and hemorrhage. AIP Neg. 89024.

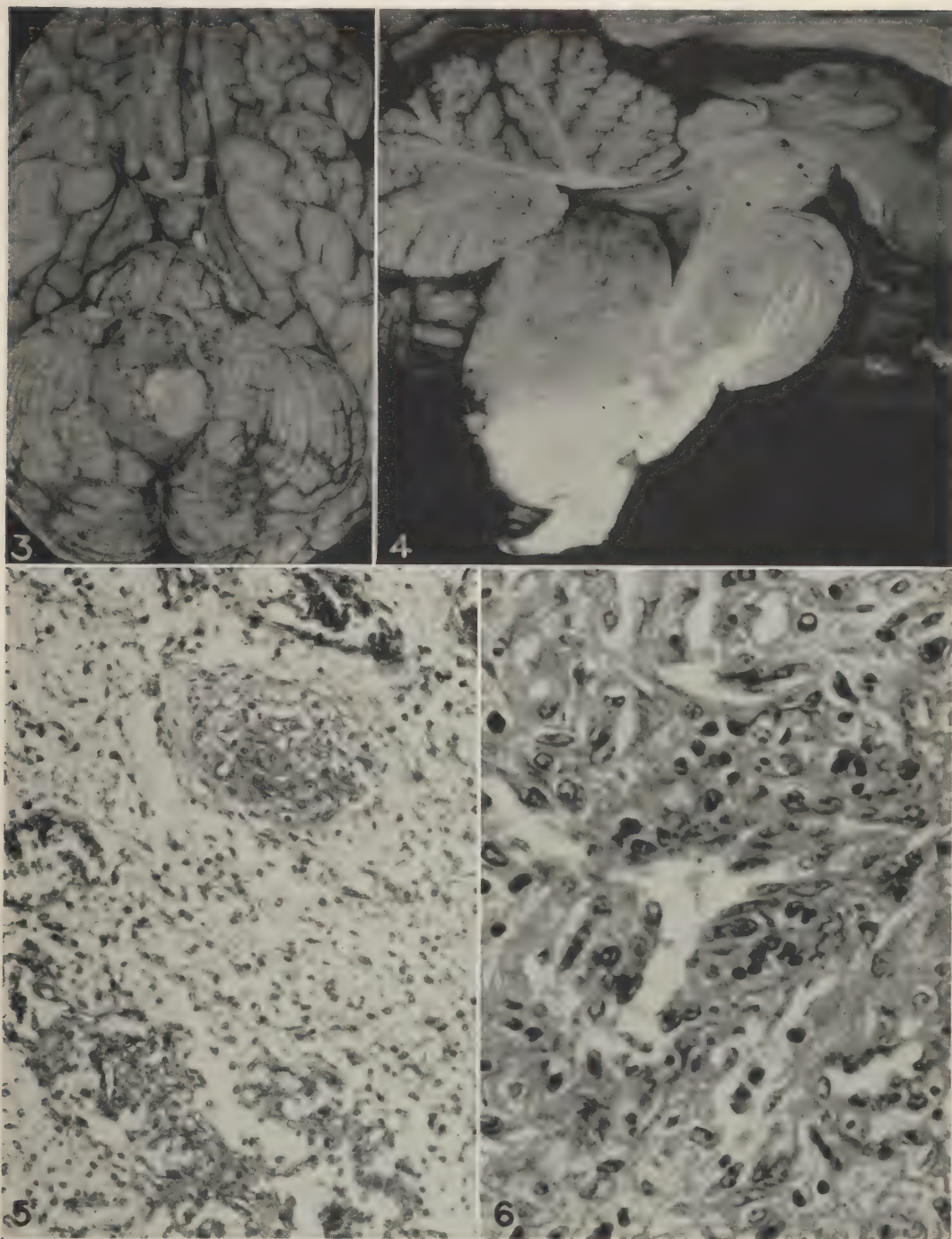


FIG. 3. Glioblastoma multiforme: Inferior surface of brain showing the tumor at the right of brain stem. AIP Neg. 89293.

FIG. 4. Longitudinal section through brain stem showing extent of lesion in Fig. 3. AIP Neg. 89294.

FIG. 5. Glioblastoma multiforme: marked vascular proliferation. $\times 200$. AIP Neg. 96243.

FIG. 6. Intimal proliferation in vessels in glioblastoma multiforme. $\times 425$. AIP Neg. 96240.

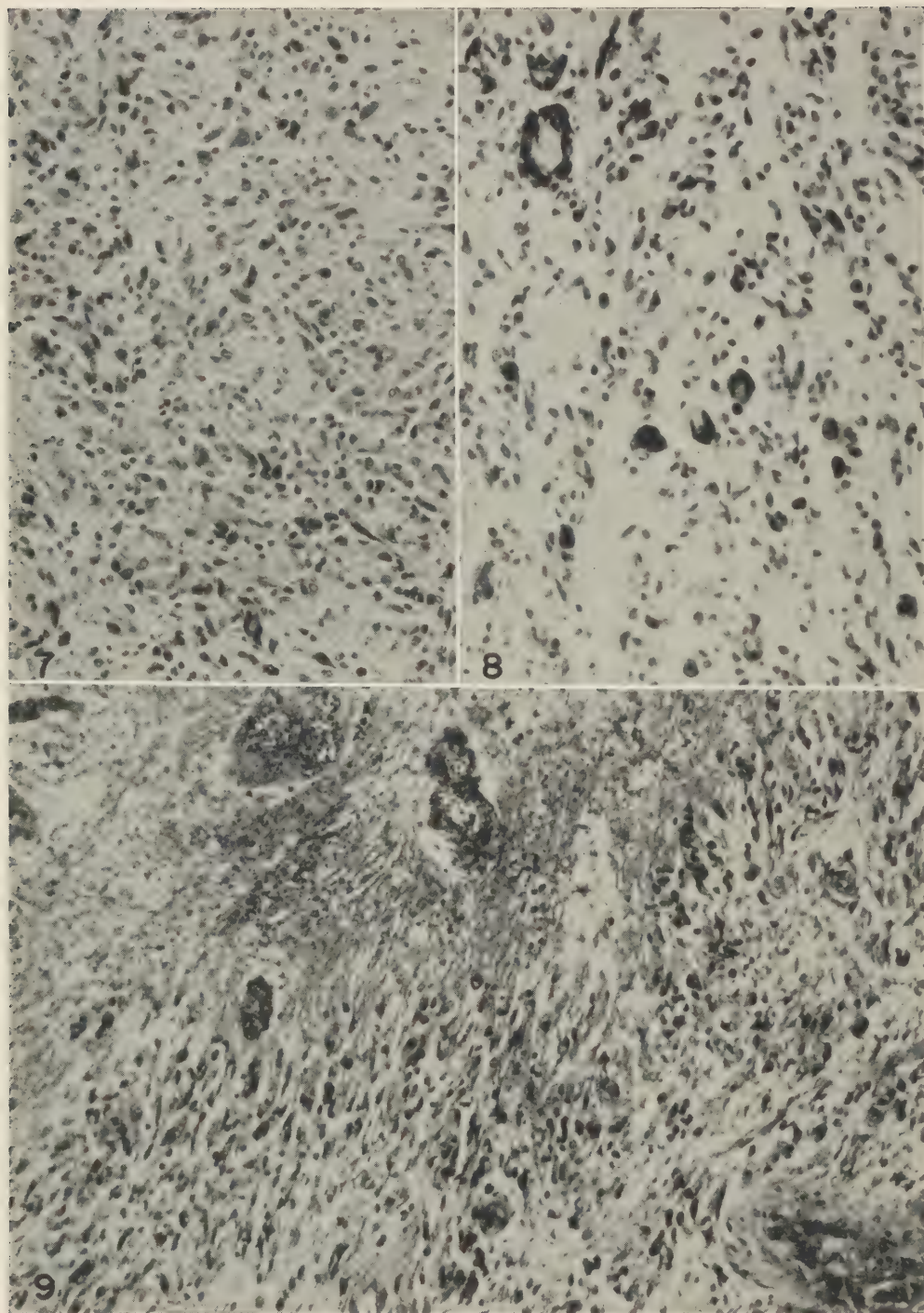


FIG. 7. Glioblastoma multiforme: marked pleomorphism with a few giant cells. $\times 205$. AIP Neg. 96244.

FIG. 8. Glioblastoma multiforme: numerous giant cells with pleomorphic spongioblasts. $\times 225$. AIP Neg. 96237.

FIG. 9. Glioblastoma multiforme with foci of necrosis and pseudopalisading of surrounding pleomorphic cells. $\times 175$. AIP Neg. 96236.

vessels is apparent, and the cells of both adventitia and intima undergo proliferation. At a later stage the walls of the vessels may become hyalinized. The rupture of some vessels, and obliteration by endothelial proliferation with subsequent infarction, accounts for the frequent hemorrhages and areas of necrosis seen in this tumor (Fig. 9).

The vascular processes have two distinct phases: one, new formation of vessels with many thin-walled capillaries, the other, proliferation of the cells of the intima and adventitia. The lumens of the vessels may be filled with cells arising from the intima. At times formation of papillary masses traversed by numerous vessels gives rise to a "glomeruloid" appearance. The nature of the vascular changes is uncertain, some consider them a reaction to the tumor, others part of the neoplastic process (Fig. 6).

The brain surrounding the tumors undergoes a slight gliosis characterized by large plump astrocytes and proliferation of the glial mesh work. Satellitosis may be marked.

Elvidge, Penfield and Cone⁹ have outlined the histologic features of glioblastoma multiforme as follows:

Constant findings:

- 1. Type cell, spongioblasts
- 2. Plump astrocytes
- 3. Tumor giant cells
- 4. Areas of necrosis
- 5. Proliferation of vascular endothelium
- 6. Mitosis
- 7. Fibroblastic overgrowth

Probably constant findings:

- 1. Increased vascularity
- 2. Adventitial proliferation

Frequent findings:

- 1. Cyst formation, small
- 2. Neighborhood glial reaction, satellitosis

The glioblastomas usually occur in the telencephalon, involving the cerebral cortex. The locations of those in this series are as shown at the top of the next column.

More than one lobe was involved in 10 cases. Seventy-three of the 102 glioblastomas extended into neighboring areas, but the site

	Right	Left	Side Not Mentioned
Frontal lobe	20	9	
Parietal lobe	16	10	2
Temporal lobe	7	12	
Occipital lobe	2	1	
Cerebellum	1	1	1
3rd ventricle	4		
4th ventricle	2		
Pons	4	4	
Midbrain	1		
Quadrigeminal Plate	1		
Thalamus	1		
Left cerebrum	1		
Corpus callosum	1		
Medulla	2		
Basal ganglion	2	5	
	—	—	—
Total:	65	42	3

of maximum growth is as given above. In 2 cases implants were present in the ventricle some distance from the original growth. In one other the white matter of the entire left hemisphere was involved.

The duration from onset of symptoms to diagnosis is as follows:

	Number	Per Cent
Less than 1 month	40	39.2
1-2 months	14	13.7
3-5 months	25	24.5
6-12 months	12	11.8
1-2 years	9	8.8
Unknown	2	2.0
	—	—
	102	100.0

In 84 per cent of cases symptoms had been present for less than 6 months; in 54 per cent, less than 2 months. The duration of symptoms of patients from 18 to 20 years of age was especially short not exceeding 6 weeks in any case. Previous trauma was reported in 10 of the 102 cases.

Papilledema took precedence over headache as the most frequent symptom; it occurred in 90 cases, headache in 81. There was a multiplicity of other symptoms including unconsciousness in 19 cases; hemiparesis on the right in 15, on the left in 6; hemiplegia of the right in 12, of the left in 2; nausea and vomiting in 16; mental changes in 14; diplopia in 14; failing vision in 12; dizziness in 12, diffi-

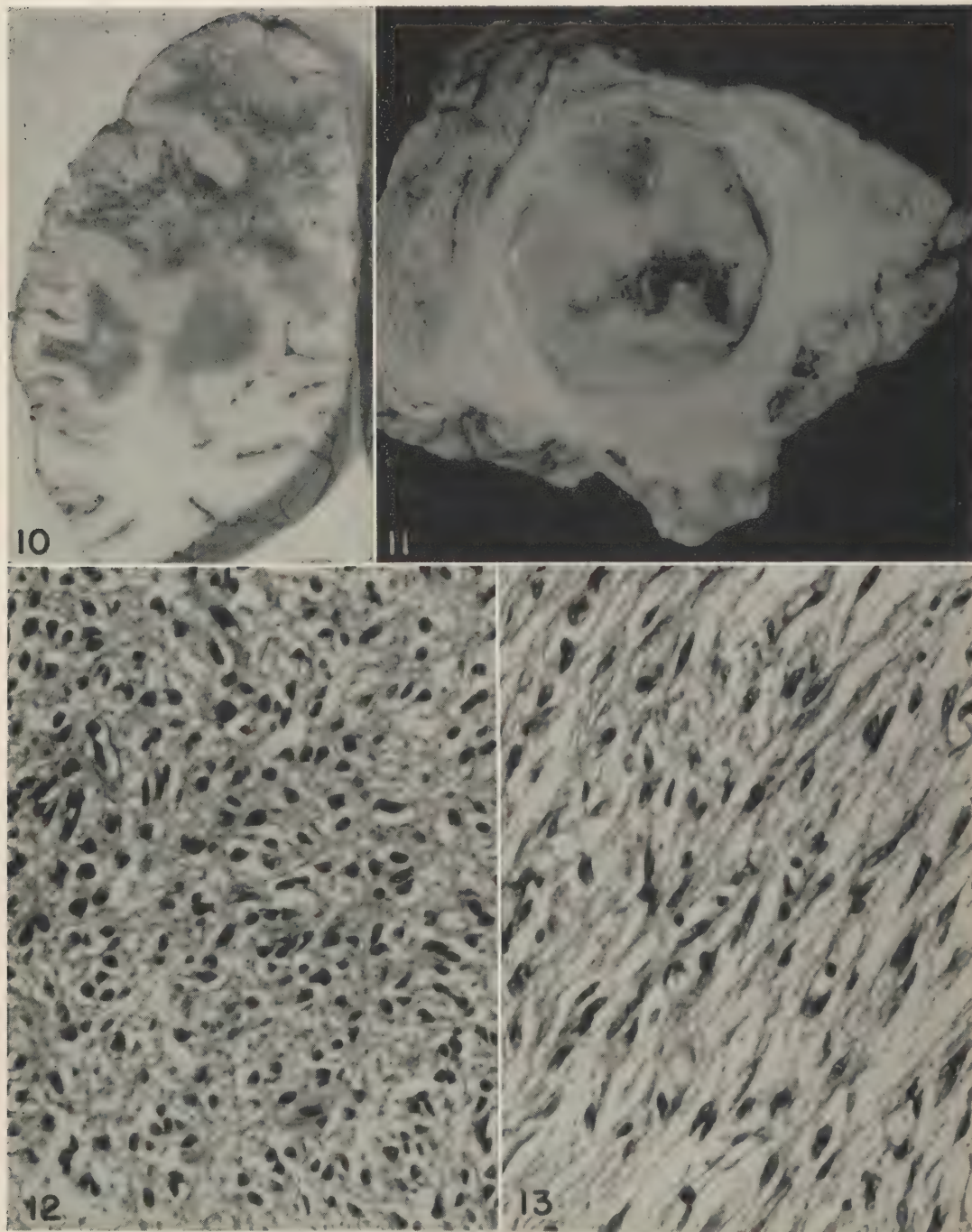


FIG. 10. Astrocytoma frontal lobe with no distinct line of demarcation. AIP Neg. 77738.

FIG. 11. Astrocytoma in 4th ventricle containing hemorrhage. AIP Neg. 96368.

FIG. 12. Astrocytoma showing small stellate cells with short processes. $\times 250$. AIP Neg. 96224.

FIG. 13. Astrocytoma, fibrillary type. $\times 405$. AIP Neg. 96229.

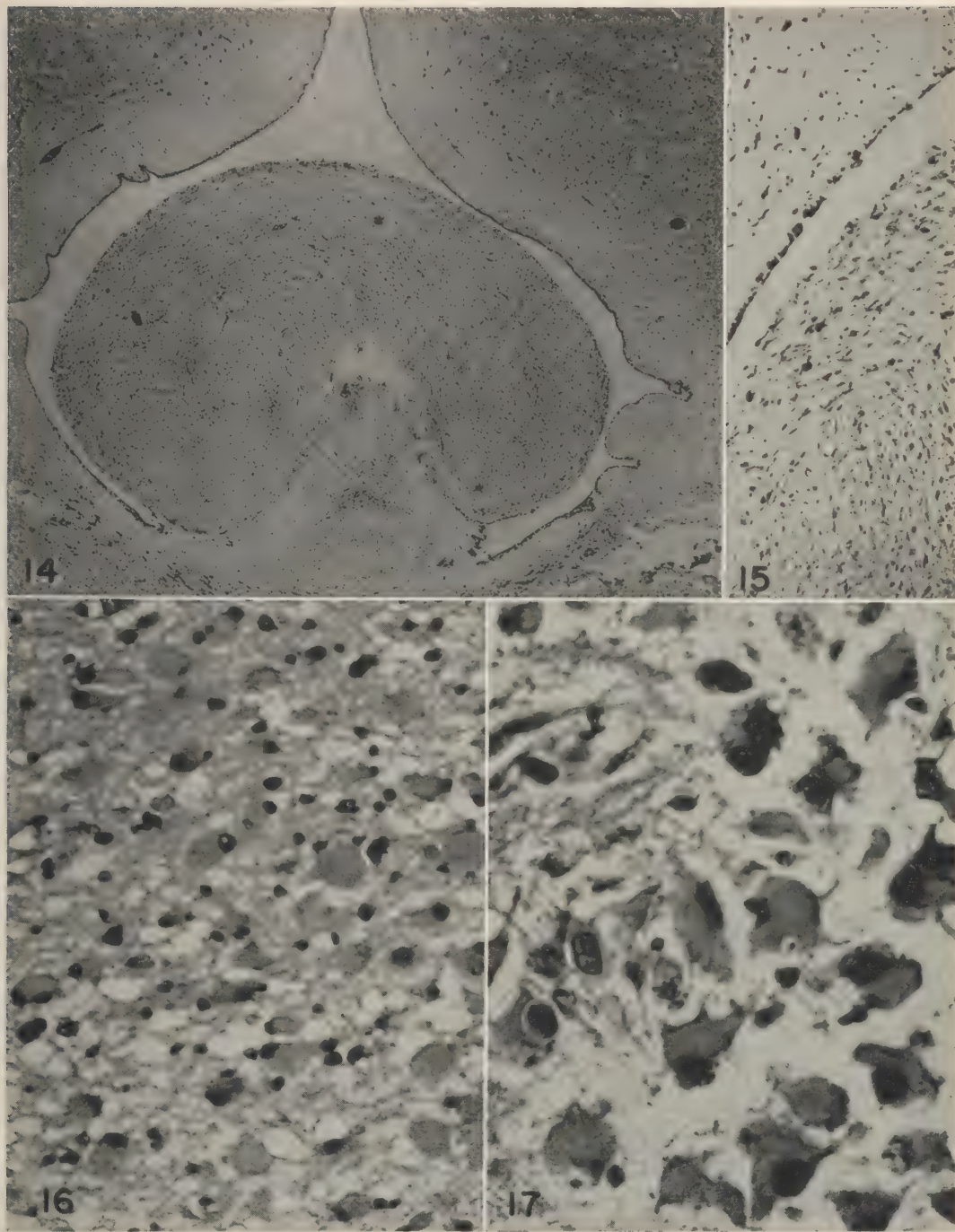


FIG. 14. Astrocytoma in aqueduct of Sylvius. $\times 25$. AIP Neg. 93355.

FIG. 15. Astrocytoma showing spindle cells. Same as Fig. 14. $\times 150$. AIP Neg. 93353.

FIG. 16. Astrocytoma characterized by plump "gemistocytic" astrocytes. $\times 250$. AIP Neg. 96280.

FIG. 17. "Gemistocytic" astrocytoma. Note the persistence of some processes. $\times 605$. AIP Neg. 96279.

culty in speech in 7; nervousness in 6; tingling in 5; lethargy in 5; stupor in 5; numbness, general weakness, syncope, aphasia, drowsiness, and convulsions, each observed in 4; coma in 3; blindness, ataxia, difficulty in swallowing and general tremor in 2 each, and quadriplegia in 1. No symptoms were noted in 5 cases, and sudden death occurred in 5 others.

Craniotomy was performed in 76 cases; in the remaining 26 there was no operation. Ventriculograms were done in 53 and encephalograms in 10. Only 22 of the patients were able to leave the hospital after craniotomy. Four deaths occurred after spinal puncture, 6 after ventriculogram. Sixteen deaths occurred the day of the operation; 14 from 2 days to 3 months after admission without operation.

The intervals between operation and death are listed:

Deaths	Number	Per Cent
On table	1	2.0
Less than 1 day	6	12.0
1-7 days	19	38.0
2-4 weeks	7	14.0
2-5 months	11	22.0
6-8 months	6	12.0
	50	100.0

Multiple operations were performed in 6 cases.

Irradiation therapy was given 10 of the 23 patients who are alive at this time.*

The clinical diagnosis varied, as in all other intracranial neoplasms, but "brain tumor" was specified in 83 cases. Cerebrovascular accident was recorded in 5, brain abscess in 3, encephalitis in 2, metastatic lesion, tuberculous meningitis, acute sclerosis, psychosis, and alcoholic neuritis in one case each. Four cases were undiagnosed.

The correct localization of the lesion was made in 42 cases.

Astrocytoma: Sixty-three astrocytomas of various types made up 14.1 per cent of the intracranial neoplasms and 22.6 per cent of gliomas. Sixty astrocytomas were in males and 3 in females; 59 of the patients were white, 3

Negro, and 1 Chinese; the average age was 26.5 years.

The gross appearance of the lesion is that of an infiltrating tumor containing foci of degeneration with formation of cysts. The solid variety of astrocytoma is not sharply demarcated; about two-thirds are of this kind; they are gray-white, firm, rubbery and slightly elevated. The cystic astrocytoma usually has a firm, white, rubbery mural nodule in the periphery of the cyst; in spite of its infiltrative nature it appears grossly to be well circumscribed (Fig. 10 and 11). The rubbery consistency of astrocytomas is due to the concentration of neuroglia fibers.

Microscopically the astrocytomas are classified as fibrillary, protoplasmic, pilocytic (piloid or hair-like), gemistocytic, or diffuse. Courville⁶ described only two varieties, fibrillary and protoplasmic. The fibrillary astrocytoma is composed of widely separated cell bodies with long intertwining processes (Fig. 12). The protoplasmic variety is made up of cells with lack of detail in the intercellular substance. In the pilocytic variety the processes are elongated and "hair-like;" the cells are widely separated, and the meshwork, in which the pilocytic fibrils run in parallel bundles, is less dense (Fig. 13-15). Cysts are frequently seen with liquefaction necrosis of fibrils. The gemistocytic, or bloated cell variety, contains large plump eosinophilic cells (with hematoxylin-eosin stain) (Fig. 16 and 17). The fibrils of the gemistocytic cells are short; the nucleus is large, and the cell body is filled with homogeneous cytoplasm. An occasional cell may have multiple nuclei. Gemistocytic cells may occur in any form of astrocytoma and are frequently seen in reactive gliosis. The diffuse astrocytoma is composed of numerous small nuclei of equal size scattered diffusely throughout the brain tissue. The cells are stellate and appear to be in various stages of development from the astroblast to the mature astrocyte. This tumor has no boundaries (Fig. 18-23).

Astrocytomas may develop anywhere throughout the brain where glial supportive elements are present. The locations of 63 astrocytomas were as follows:

* The final revision of this paper was made in June, 1946. All statements concerning length of survival refer to this date.

Location	Number of Cases	Per cent of Astrocytomas
Frontal lobe	22 (Right 10, Left 2)	34.9
Temporal lobe	14 (Right 8, Left 6)	22.2
Parietal lobe	9 (Right 5, Left 4)	14.2
3rd ventricle	5	7.9
Cerebellum	4 (Right 2, Left 2)	6.4
Midline cerebellum	3	4.8
Pons	2	3.2
Pineal region	2	3.2
Unknown	2	3.2
Total:	63	100.00

Astrocytomas in the military age group show no predilection for a particular side of the brain, but a striking one for the frontal, parietal and temporal lobes. Fourteen of the tumors had spread into the surrounding structures involving more than one lobe of the brain; the exact point of origin could not be determined because of the size of the lesions, hence they were considered to be located in the area where the maximum amount of tumor was found. One astrocytoma was implanted in the 3rd ventricle some distance from the original tumor in the temporal lobe.

The duration of symptoms of the astrocytomas calculated from onset to diagnosis varied from less than 1 week to 3 years. Details are as follows:

Duration	Number of Cases	Per Cent
Less than 1 month	13	20.6
1-2 months	9	14.3
3-5 months	15	23.8
6-12 months	15	23.8
Over 1 year	9	14.3
Unknown	2	3.2
Total:	63	100.0

The duration of 37, or 58.7 per cent of the tumors, was under 6 months. One astrocytoma of unknown duration was found in the aqueduct of Sylvius in the brain of a suicide who had no previous history indicating the presence of a brain tumor.

The most constant symptom at the time of diagnosis was headache which occurred in 47 cases. Next in frequency was papilledema in 27, nystagmus in 19, nausea and vomiting in 19, convulsions in 10, dizziness in 9, decreased vision in 9, blurring of vision in 8,

stupor, syncope, coma, and hemiplegia in 4 each, hemiparesis in 3, diplopia in 2, blindness in 2; sudden death occurred once. Multiple symptoms were present in many cases.

Craniotomy was performed on 54 patients and was preceded by ventriculogram or encephalogram in 35. Two patients died 1 day after ventriculogram without further operation. Nine deaths occurred less than 1 day after operation, 8 after 1 day, 7 in less than 1 week, and 5 in less than 1 month. The remaining deaths occurred 3 and 5 months after operation. All of the deaths were directly related to the surgical procedure. In 5 cases death occurred before operation could be performed. In 25, follow-up studies have not been completed, but at the last review of the histories no recurrences or deaths were noted.

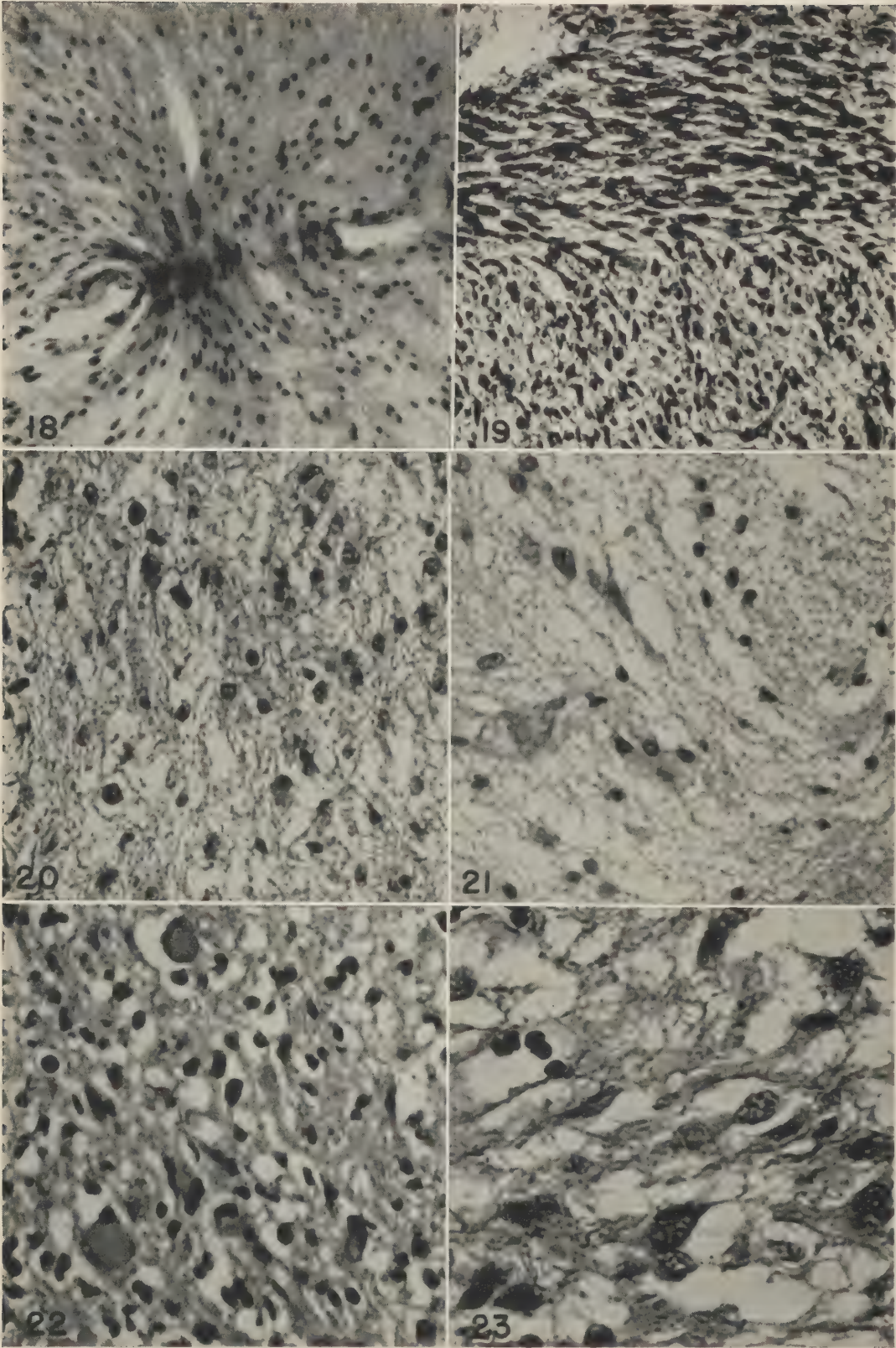
In 3 cases subsequent craniotomies were necessary to alleviate symptoms, and in 1 of these, 3 operations were performed before death occurred. Irradiation treatment was employed in 5 cases.

The diagnosis of brain tumor was made in 54 cases with localization in 24. Other diagnoses were: psychosis with tumor, meningitis, meningioma, cerebral hemorrhage, pineal tumor, ruptured aneurysm, and epilepsy. No history of trauma was mentioned in any of this group.

Medulloblastoma: Forty-five intracranial neoplasms were diagnosed as medulloblastomas, making up 10.2 per cent of all the tumors, and 16.2 per cent of the gliomas. Forty occurred in white soldiers, 5 in colored. The average age in this group was 23.5 years.

Grossly, medulloblastomas are grayish red, soft, friable, solid tumors, usually located in the cerebellum in or about the midline. The margins of tumor invade the surrounding brain and meninges and often extend into ventricles with implantation on the spinal cord by way of the spinal fluid. The margins are grossly distinct though histologically the tumors are not well circumscribed (Fig. 28-30). If the tumor obstructs the ventricular system hydrocephalus results.

The microscopic appearance of the tumor is characterized by small carrot-shaped cells



FIGS. 18-23

each with a distinct elongated nucleus and scanty cytoplasm which ends in an indefinite tail. A nucleolus is sometimes seen. The cells form pseudorosettes, irregular ball-like masses, or may assume a perivascular arrangement. An occasional mitotic figure may be seen. The blood vessels are numerous but do not show any specific change. The reticulum network is usually prominent; intercellular substance is practically absent. The tumor occasionally contains neuroblastic and spongioblastic elements. In our group the latter were seen in 2 tumors while neuroblasts were prominent in 3 (Fig. 31-34).

Although medulloblastomas have a predilection for the cerebellum, they may occur elsewhere.

The locations for the 45 tumors are listed below:

Right cerebellum	19
Left cerebellum	10
Midline cerebellum	11
Pons	3
Cervical cord	1
Right temporal lobe	1
	—
	45

In the majority of the cases the spinal cord was not removed but an implant on the spinal cord was mentioned in one case. The tumors have a strong tendency to invade surrounding tissues; this was noted in 24 of our 45 cases. In several the tumor appeared to be expansile and compress the surrounding structures. The extent and location of the extension varied but it was usually into the 4th ventricle and brain stem from either side of the cerebellum. The tumor in the temporal lobe, which was surgically removed, may represent an implantation from a cerebellar lesion.

The duration of symptoms from onset to diagnosis are as follows:

Duration	Number of Cases	Per Cent
Less than 1 month	7	15.5
1-2 months	11	24.4
3-5 months	11	24.4
6-12 months	12	26.8
Over 1 year	1	2.2
Unknown	3	6.7
	—	—
Total:	45	100.0

In 36, or 85.7 per cent, of the 42 cases in which duration was noted it was less than 7 months, and in 29, or 69 per cent, less than 4 months.

Numerous signs and symptoms, most of them related to the cerebellum, were caused by medulloblastomas. Again headache was the most frequent, being present in 36; staggering gait (ataxia) was noticed in 26, as well as papilledema in 25. Vertigo was reported in 14, vomiting in 14, stiff neck in 11, nystagmus in 10, nausea in 9, hemiparesis in 7, diplopia, pain in the neck, drowsiness, blurring vision in 5 each, projectile vomiting in 4, hemiplegia, tinnitus, syncope, loss of vision, coma, and deafness in 2 each. Homonymous hemianopsia, areflexia, slurring speech, 6th nerve palsy, personality changes, uncinat fits, and exophthalmos were each noted in 1 case.

One history recorded the fact that the patient's brother had died of medulloblastoma. Hydrocephalus was diagnosed in 15 cases following encephalogram or ventriculogram. Craniotomy was resorted to in 25 of the 45 cases of medulloblastoma. Ventriculograms in 20 cases confirmed the diagnosis of a lesion of the posterior fossa.

Of the 27 on whom operation or biopsy was performed, 10 died within 24 hours, one 3 and another 6 days after operation. One lived for 5 months, another for 8 months, and 3 were still living 3 months after craniotomy. As far as is known, 11 are still alive,

FIG. 18. Astrocytoma—fibrillary type. $\times 30$. AIP Neg. 96157.

FIG. 19. Astrocytoma—protoplasmic type. $\times 330$. AIP Neg. 96277.

FIG. 20. Astrocytoma—pilocytic type. $\times 330$. AIP Neg. 96228.

FIG. 21. Astrocytoma—pilocytic type. $\times 550$. AIP Neg. 96156.

FIG. 22. Astrocytoma—mixed type, with numerous plump astrocytes. $\times 210$. AIP Neg. 96253.

FIG. 23. Astrocytoma showing processes, some of which are attached to blood vessels. AIP Neg. 96276.

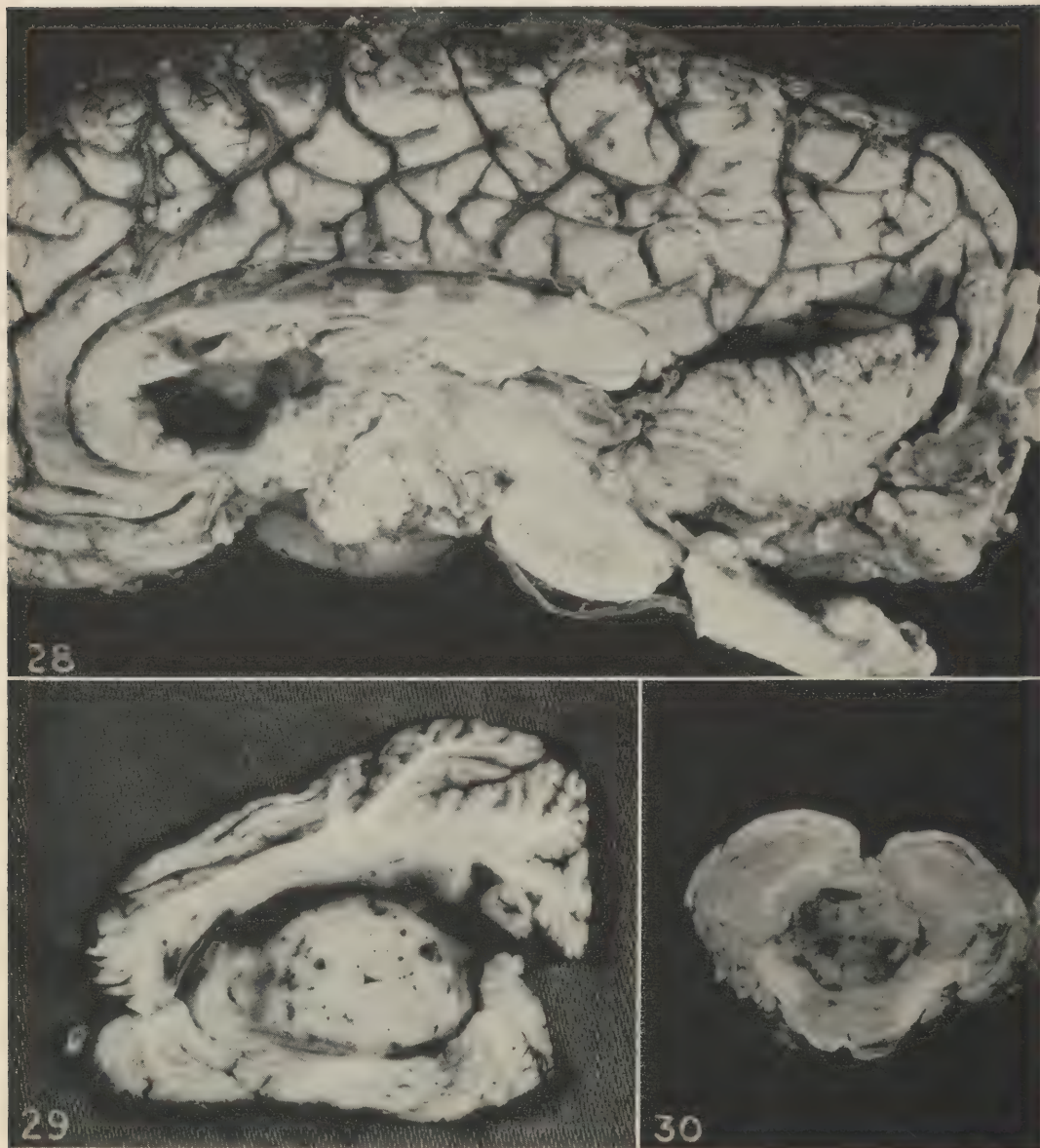


FIG. 28. Medulloblastoma of cerebellum with extension into brain stem and implantation along ventricular surface. AIP 130099.

FIG. 29. Medulloblastoma arising in right lobe of cerebellum. AIP Neg. 84635.

FIG. 30. Medulloblastoma of cerebellum obliterating the 4th ventricle. AIP Neg. 96364.

and 7 of these have had irradiation treatment. Five patients died following ventriculogram before a craniotomy was done; 8 died suddenly before any surgical measures could be employed, 1 of these during a Metrazol treatment for convulsions.

Multiple operations, up to 3 in number, were performed in 3 cases.

In 15 cases the diagnosis was intracranial

neoplasm; in 4, tumor of the posterior fossa; in 16, cerebellar tumor, with the side involved mentioned in 6. Psychosis was diagnosed in 7. Cerebral hemorrhage, multiple sclerosis, cord tumor, and psychosis due to tumor were other diagnoses. Trauma occurring from 3 months to 11 years previously was mentioned in 5 cases.

Astroblastoma: Six of the 446 intracranial

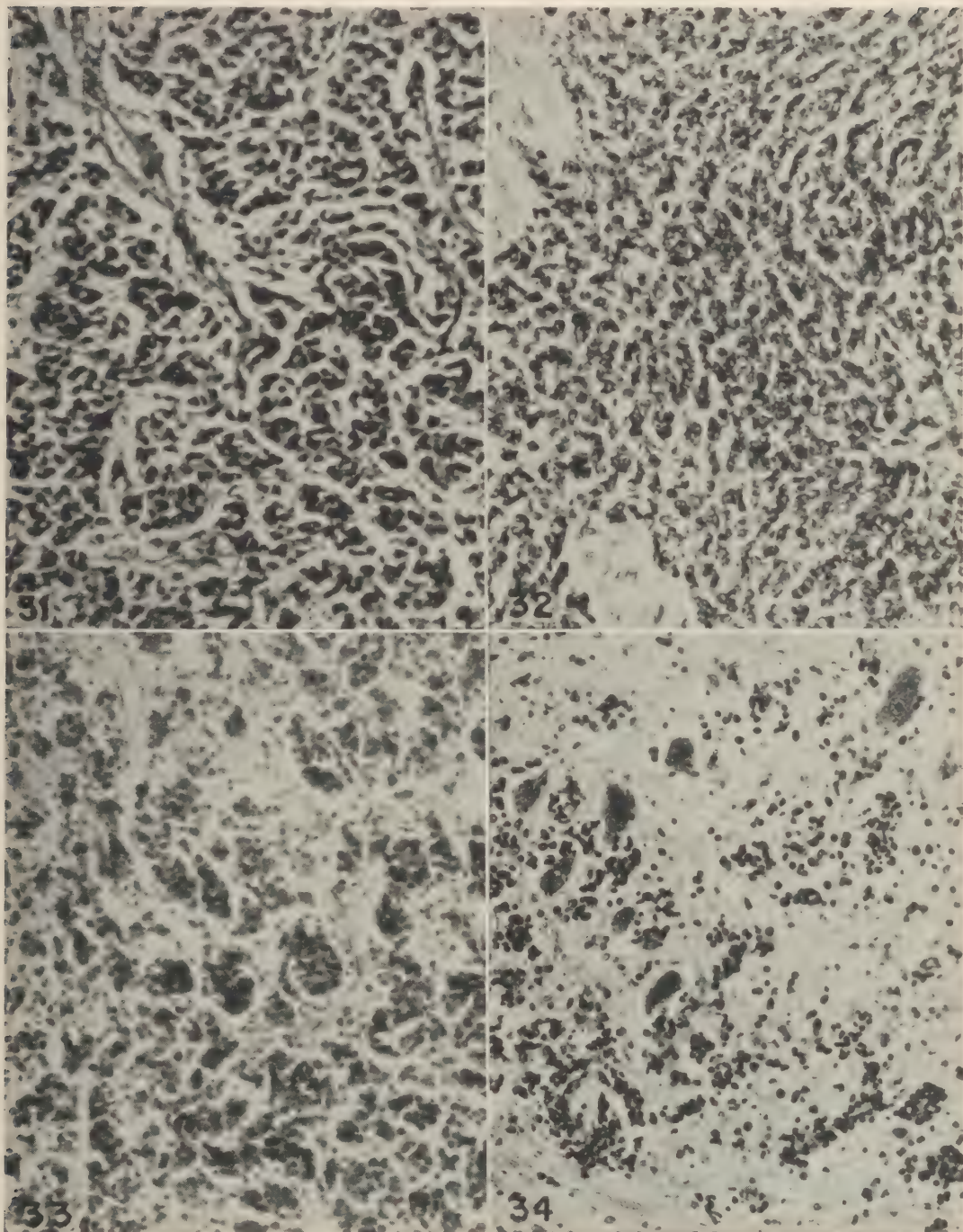


FIG. 31. Medulloblastoma showing fine vascular stroma. The cytoplasm is scanty about the nuclei of many cells. $\times 220$. AIP Neg. 96271.

FIG. 32. Medulloblastoma made up of cells with more granular nuclei than is usually seen. These resemble neuroblasts. $\times 230$. AIP Neg. 96267.

FIG. 33. Medulloblastoma with numerous pseudorosettes and clumps of small hyperchromatic cells. $\times 250$. AIP Neg. 96270.

FIG. 34. Medulloblastoma invading cerebral cortex. Note the nerve cells with typical Nissl's granules. $\times 175$. AIP Neg. 96265.

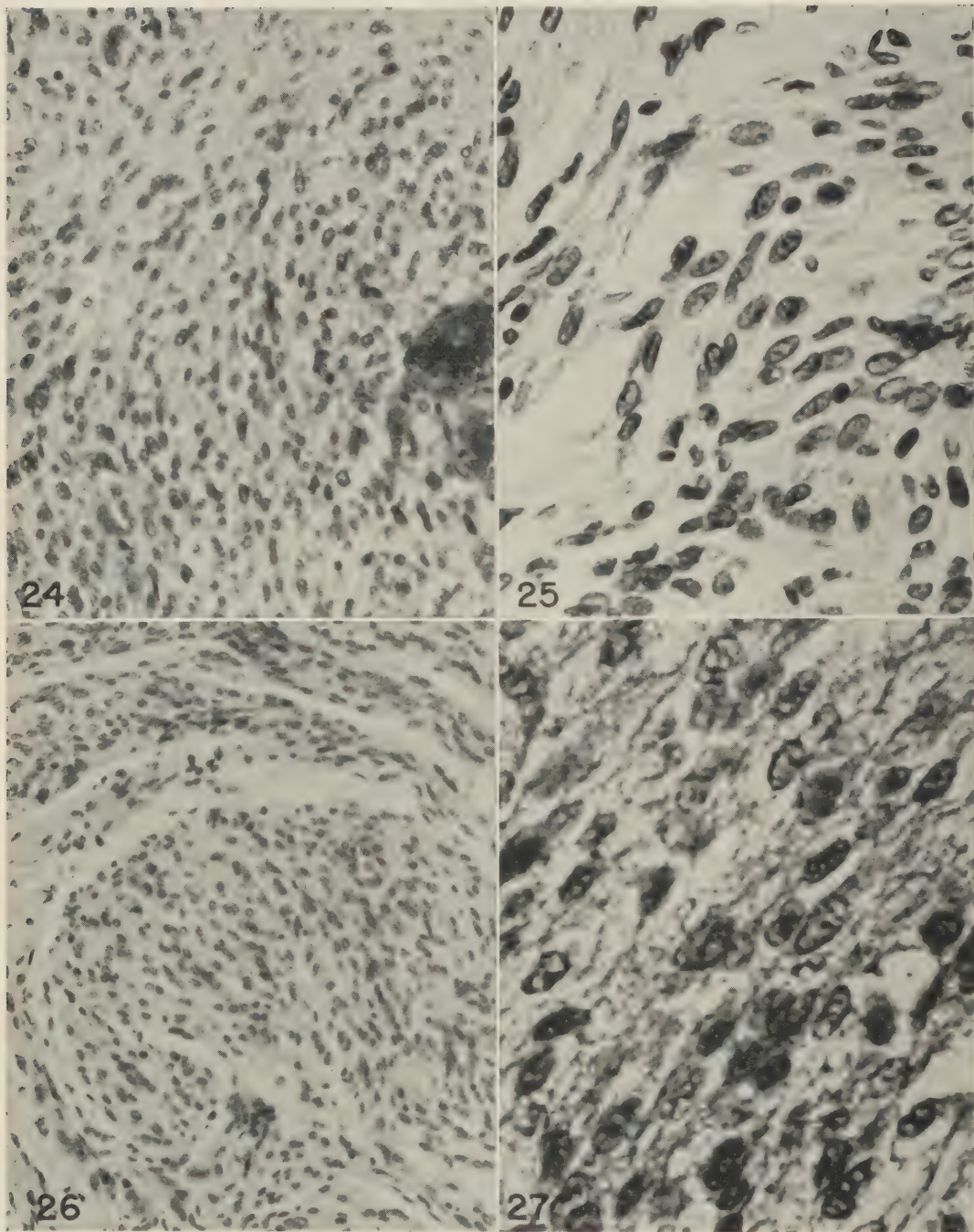


FIG. 24. Spongioblastoma polare showing cellularity and a few giant forms. $\times 310$. AIP Neg. 96273.

FIG. 25. Spongioblastoma polare. Higher magnification emphasizes characteristic cells. $\times 650$. AIP Neg. 96161.

FIG. 26. Spongioblastoma polare consisting of unipolar and bipolar spongioblasts; often classified as astrocytoma. $\times 230$. AIP Neg. 96160.

FIG. 27. Processes of spongioblasts are distinct. (Same as Fig. 16.) $\times 900$. AIP Neg. 96274.

neoplasms were classified as astroblastomas, representing 1.3 per cent of the series and 2.2 per cent of gliomas. All these tumors were in males, 5 of them white, one Negro. The ages of the patients were 21, 22, 23, 24, 25, and 37, averaging 25.1 years.

Grossly the tumors vary greatly and may lie either superficially or deep in the brain substance. They are usually poorly circumscribed and infiltrate the surrounding tissue. Hemorrhage and cystic degeneration are common. These tumors are probably transitional between astrocytoma and glioblastoma multiforme, differentiating in the astrocytic direction.

The cellular components vary from mature astrocytic elements to immature spongioblasts. The typical cell is roughly triangular in shape, and has an abundant cytoplasm with one or more nuclei. There are often well-defined processes or "sucker feet" which extend to the vessels. These processes appear as single, thick expansions which attach to or abut against the blood vessel. Multinucleated cells are not uncommon. Atypical mitotic figures are rarely seen. In some of the tumors endothelial proliferation is marked. The perivascular connective tissue is increased in amount; condensation of fibrils about the thin-walled vessels is characteristic.

Four of the 6 astroblastomas were located in the parietal lobes, the others in the temporal and occipital lobes of the cerebral cortex. All had invaded the surrounding structures, 3 had extended into the ventricles. The largest tumor appeared to involve the entire left cerebral hemisphere.

The duration from the onset of symptoms to date of diagnosis ranged from 1 day to 5 years. In 2 the symptoms were present less than 3 months, in 1 of these less than 1 month.

Headache was present in all cases; otherwise the symptoms were varied. In 1 an initial sudden attack of unconsciousness was the only sign of a brain tumor. Weakness, vertigo, ataxia, blurring vision, diplopia, stupor, and tremor were most often found at the initial examination. One patient had left hemiplegia

which was of sudden onset. Roentgenograms showed calcification of 1 tumor. Trauma was not mentioned in any of the cases. The clinical diagnosis of brain tumor was made in 5 of the 6 cases; in the only one undiagnosed the patient was comatose on admission.

Craniotomy was performed in 4 cases; in the other 2 death occurred before operation could be performed. Craniotomy had been done previously in 2 cases, each having had 2 operations at an interval of about 3 months. One patient died 1 day after operation while no follow-ups are recorded on the other 3.

Spongioblastoma polare: Thirteen examples of spongioblastoma polare were observed in the series, representing 2.9 per cent of all the tumors and 4.6 per cent of the gliomas. Twelve were in males and 1 in a female; 4 of the patients were Negroes. The average age was 25.3 years.

The gross appearance of this tumor is subject to wide variation. It is usually well demarcated, gray and firm, with foci of degeneration, and cyst formation. Spongioblastoma polare frequently occurs in the pons or the brain stem and a diffuse enlargement of the pons results from infiltration by the tumor (Fig. 24-27).

Microscopically, the tumor is made up of spindle shaped spongioblasts with either bipolar or unipolar processes. The cells are piriform to spindle in shape, their processes are long and thick, often wavy, and in parallel rows. The nuclei are elongated and vesicular. An occasional mitotic figure may be seen. In 2 tumors astrocytes dominated the picture in association with large numbers of bipolar spongioblasts. Another tumor was primarily a spongioblastoma polare with foci of glioblastoma multiforme.

Spongioblastoma polare, like many others of neuroectodermal origin, is usually mixed and rarely of pure type; some authors classify it as a variety of astrocytoma.

Spongioblastoma polare may be located anywhere in the brain but is most frequent in the brain stem. The sites of tumor in our series are as follows:

Location	Number	Per Cent
Pons	4	30.8
Midbrain	1	7.7
3rd ventricle	3	23.1
Pineal body	1	7.7
Thalamus	1	7.7
Occipital lobe	1	7.7
Temporal lobe	1	7.7
Cerebellum	1	7.6
	<hr/>	<hr/>
	13	100.0

The tumor was locally infiltrative and extended imperceptibly into surrounding tissues. There was great variation in size; tumors in the pons were smaller but caused symptoms earlier than those in the cerebral cortex. From the pons the tumors extended into the medulla oblongata, brachium pontis and cervical cord; those in the 3rd ventricle infiltrated the chiasm, thalamus, and basal nucleus. The tumor in the midbrain surrounded the aqueduct of Sylvius.

The interval from onset of symptoms to diagnosis varied from a few days to 18 months.

	Number of Cases	Per Cent
Under 1 week	3	23.0
2-6 months	2	15.4
7-12 months	5	38.5
Over 1 year	2	15.4
Not given	1	7.7
	<hr/>	<hr/>
	13	100.0

It is of interest that in the 4 cases in which the interval was shortest the tumor was situated in the pons or midbrain, whereas the symptoms caused by tumors in other locations progressed more slowly.

The symptoms varied from a severe headache to coma. Headache was absent in only 2 cases; other symptoms in order of frequency were: vomiting in 6, papilledema in 5, coma in 4, impaired vision in 3, convulsions, diplopia, bulbar palsy, hemiparesis, ataxia and hypesthesia in 2 each and single instances of apathy, tremor, areflexia, paraplegia, exophthalmia, dysarthria, vertigo, nystagmus, and tinnitus.

Roentgenograms showed calcium deposits in the pituitary and pineal glands in 2 cases and erosion of the sella turcica in another; in

9 cases there was hydrocephalus.

Craniotomy was performed in 7 cases; in an eight death took place after the encephalogram and before craniotomy could be performed. At the time of this writing 3 patients are believed to be still alive although there has been no follow-up; 2 died one day post-operatively, while 2 others died 5 months after operation. Mortality statistics are necessarily incomplete so soon after the end of the war.

The clinical diagnosis was recorded in 12 cases. The location in the pons was recognized clinically in 5 cases and confirmed at post mortem in 4. The diagnosis of "encephalitis versus tumor" was made in 1 case, and "brain tumor" in the others. Sudden coma suggested "phenobarbital poisoning" in one case.

Oligodendroglioma: Fourteen of the tumors were classified as oligodendrogliomas, comprising 5.0 per cent of the group of gliomas, and 3.2 per cent of intracranial tumors. All occurred in males, 12 of them white and 2 Negro, with an average age of 27.9 years.

The tumor is usually solid, well circumscribed, and gray-red. In sections through the brain the surface of the tumor is slightly elevated above the surrounding tissue. Foci of calcification are present in 32 per cent of oligodendrogliomas of this group (Fig. 35).

The cells have a distinct limiting membrane, are usually hexagonal, and when packed closely together give a "honey comb" appearance. The nuclei are small, round, hyperchromatic, and appear to be "boxed" by clear cytoplasm. Short processes from the angles of cytoplasmic wall are seen with silver carbonate stains. An immature type of the tumor, oligodendroblastoma, is made up of larger cells which are more undifferentiated. Astrocytes and ependymal cells in varying numbers may be distributed irregularly through the tumor. The vascular component is prominent. Necrosis and calcification are seen in about one-fourth of these tumors (Fig. 36-38).

Oligodendrogliomas are usually located in the cerebrum. Eight of those in this series involved adjacent portions of the brain by contiguous extension. No ventricular implants were noted.

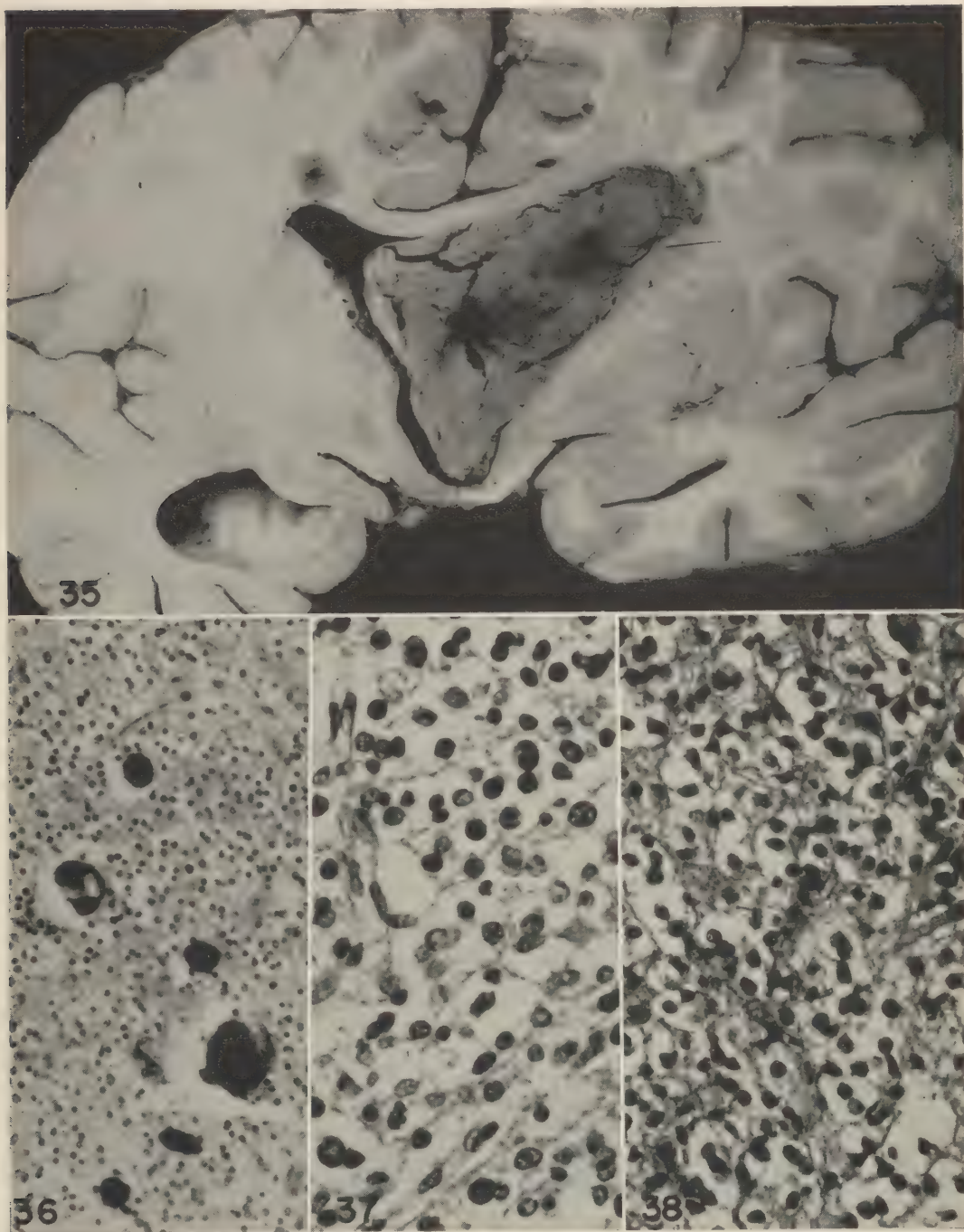


FIG. 35. Oligodendroglioma arising from the subependymal cell plate of lateral and third ventricle in the region of the foramen of Munro. AIP Neg. 85084.

FIG. 36. Oligodendroglioma with small nuclei surrounded by clear zone, giving rise to a "honeycomb" appearance. Note the flecks of calcium. $\times 100$. AIP Neg. 96268.

FIG. 37. Oligodendroglioma showing so-called "boxing in" of the nucleus. $\times 400$. AIP Neg. 75672.

FIG. 38. Oligodendroglioma: nuclei and thin cytoplasmic wall surround a clear zone. $\times 575$. AIP Neg. 96245.

The locations of the 14 oligodendrogliomas are as follows:

Frontal lobe	8
Parietal lobe	3
Temporal lobe	2
Optic chiasm (near septum pellucidum)	1

The duration of the tumor calculated from onset of symptoms to time of diagnosis varied from less than 1 week to 5 years.

Time	Number	Per Cent
Less than 1 week	1	7.1
1-3 weeks	2	14.2
1-5 months	3	21.4
6-11 months	4	28.5
1-2 years	2	14.2
Over 2 years	1	7.1
Unknown	1	7.1
	14	100.0

The presenting symptoms and signs were those of increased intracranial pressure. The most frequent symptom was headache with or without nausea and vomiting. Papilledema was seen in 8 cases. Syncope, lethargy, slurring speech, psychosis, convulsion, blurred vision, vertigo, loss of memory and coma were present separately or in combination in many of the cases.

Operation was performed in 10 cases, and death occurred in 4 of these within 3 days. Six patients were living at the last follow-up. One patient died 2, one 3, and a third 22 hours after ventriculogram; 2 expired suddenly before any surgical treatment.

The clinicians diagnosed all of the cases as brain tumor, and localized the lesion correctly in 5 of the 14. Sudden coma led to the diagnosis of aneurysm of the circle of Willis in one case.

Ependymoma: Fourteen tumors were classified as ependymomas which represent 3.2 per cent of the entire series and 5.0 per cent of gliomas. All occurred in males, 13 of whom were white and 1 a Negro, and whose average age was 26.6 years.

Grossly the tumor appears as a solid reddish brown mass. It is encapsulated, lobulated, and usually is situated near or in conjunction with a ventricle, from the surface of which it may project. Cysts are frequently seen. The cut

surface is often granular and gritty, because of flecks of calcium.

The morphologic appearance of ependymomas varies with the cytologic pattern and on this basis three varieties have been described: papillary, cellular, and epithelial. (Globus and Kuhlenbeck^{10,11} believe that papillomas of the choroid plexus should also be classed as ependymomas.)

(1) Papillary ependymomas are characterized by fibrous vascular cores surrounded by single or multiple layers of epithelium. The cells are cuboidal to columnar with large, oval, vesicular nuclei. The stroma usually is slightly myxomatous, hence the tumor is often called a myxopapillary ependymoma (Fig. 39). The epithelium does not contain mucus, unlike that of the choroid plexus tumors. So-called "blepharoplasts" seen in the cytoplasm represent the basal attachment of the cilia of the ependymal cells.

(2) The cellular ependymoma is made up of closely packed cells with abundant cytoplasm and oval nuclei containing large prominent chromatin granules. Ependymal spongioblasts may be present with the characteristic blepharoplasts. Such cells are piriform, and have heavy broad processes which terminate near a vessel, giving the appearance of pseudorosettes (Fig. 40-43).

(3) The epithelial form of ependymoma is characterized by pseudorosettes about the vessels. The ependymal cells grow side by side like cuboidal epithelium. Mitotic figures are very rarely seen (Fig. 44-47). Astrocytes and polar spongioblasts are usually scattered through ependymomas.

Although ependymomas are usually located near a ventricular surface, they may be found anywhere in the central nervous system. One of the 4th ventricle ependymomas had extended into the right cerebellum. The tumor arising from the right lateral ventricle extended into the 3rd ventricle. The cerebello-pontine angle tumor involved the caudate nucleus and the floor of the 3rd ventricle. The lesions located in the parietal, the temporal, and the frontal lobes were in close proximity to the lateral ventricles. Two of the cerebellar

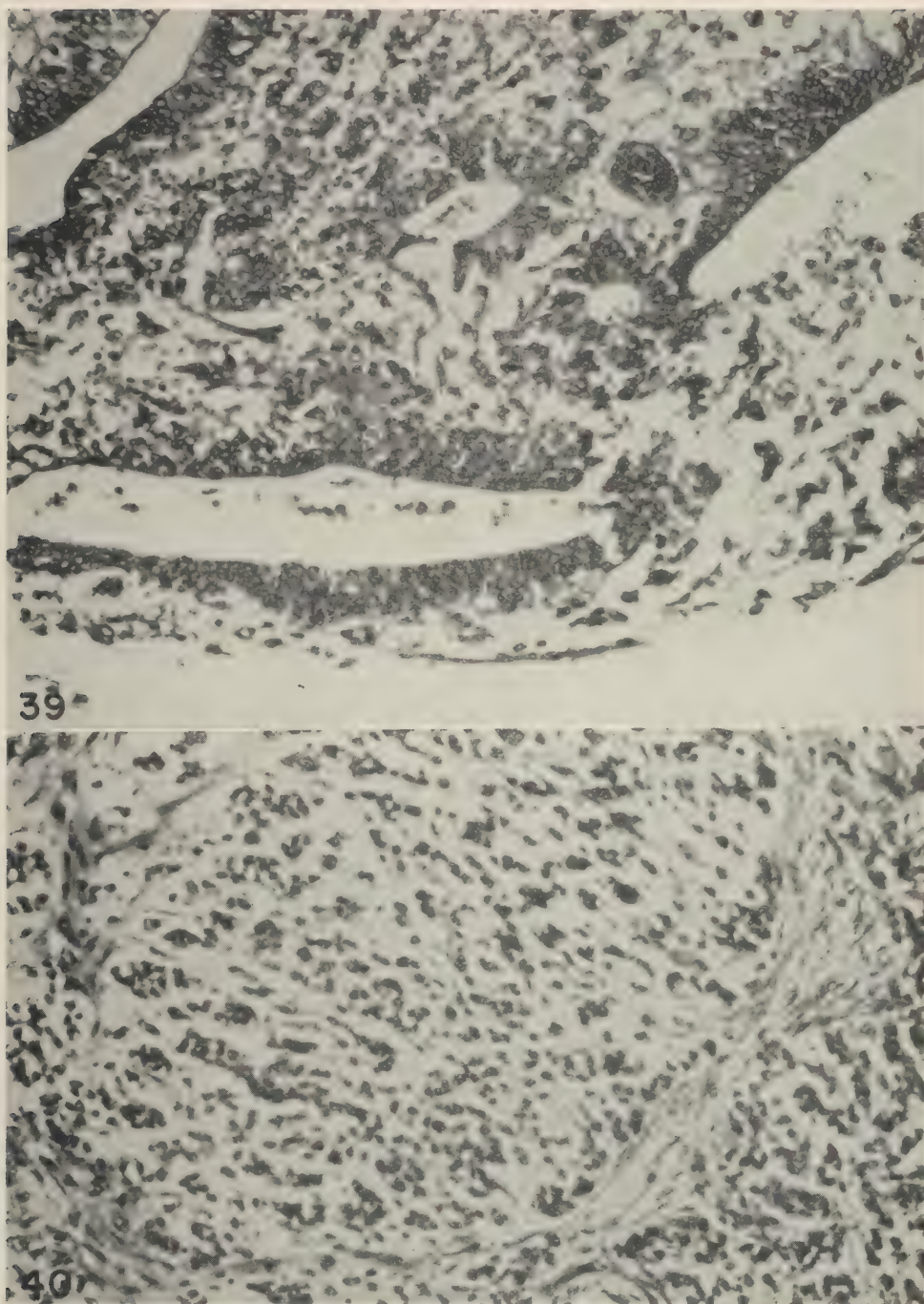


FIG. 39. Ependymoma—myxopapillary type. Note the formation of canals. $\times 230$. AIP Neg. 96185.

FIG. 40. Ependymoma—cellular type. $\times 250$. AIP Neg. 96168.

lesions had extended into the 4th ventricle. The two lesions arising in the region of the infundibulum had encroached on and incorporated the optic chiasm. The lesion in the aque-

duct remained localized. The duration of symptoms in cases of ependymoma varied from 3 weeks to 2 years. Two cases were found for each of the following durations: 3 weeks, 4

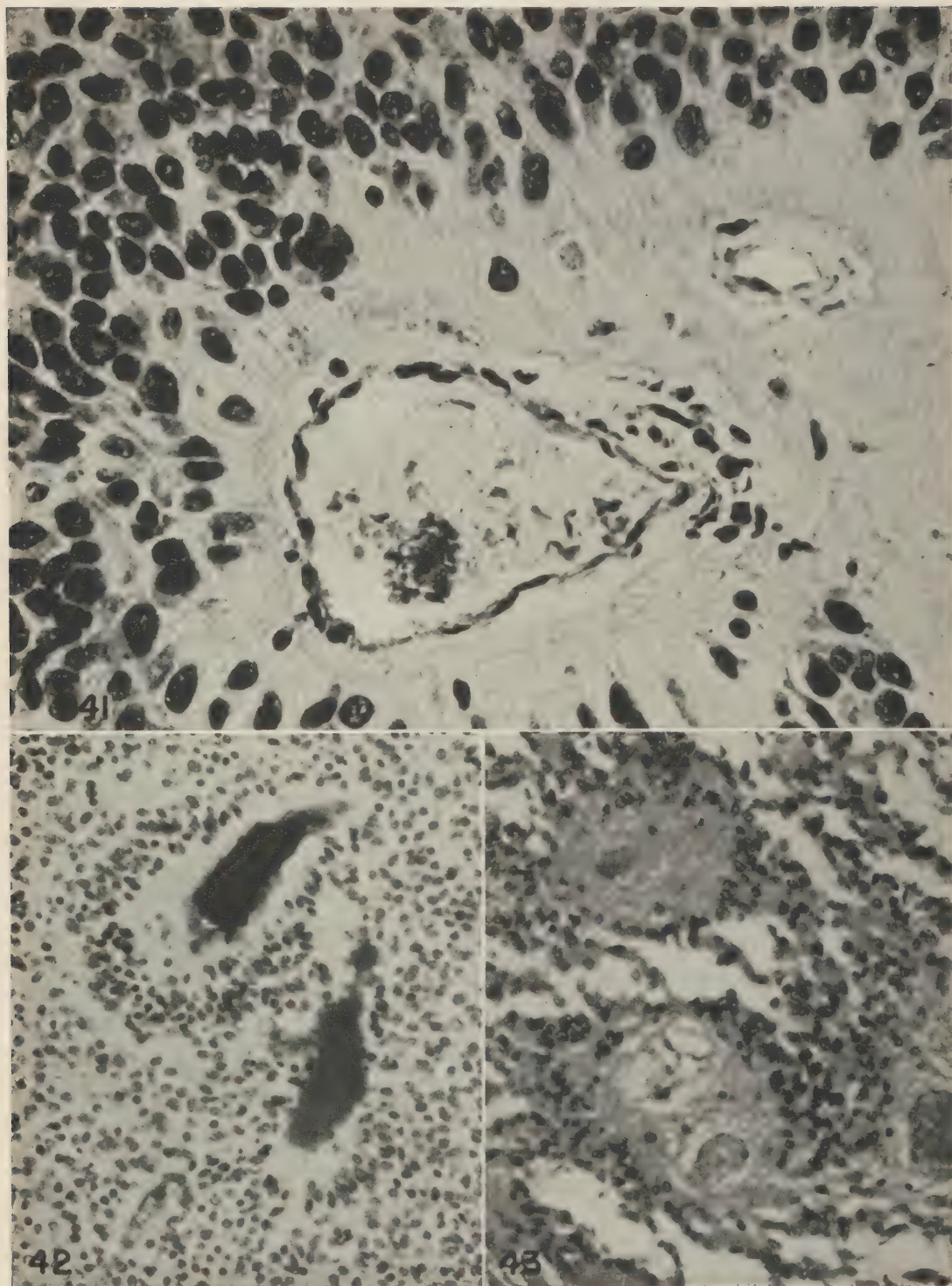


FIG. 41. Ependymoma showing the pattern of cells about the blood vessels. $\times 650$. AIP Neg. 96184.

FIG. 42. Ependymoma of cellular type with accumulation of cells about vessels and a relatively clear zone between the vessels and the cell bodies. $\times 305$. AIP Neg. 96183.

FIG. 43. Ependymoma demonstrating a variation in cellular pattern about vessels. $\times 230$. AIP Neg. 96178.

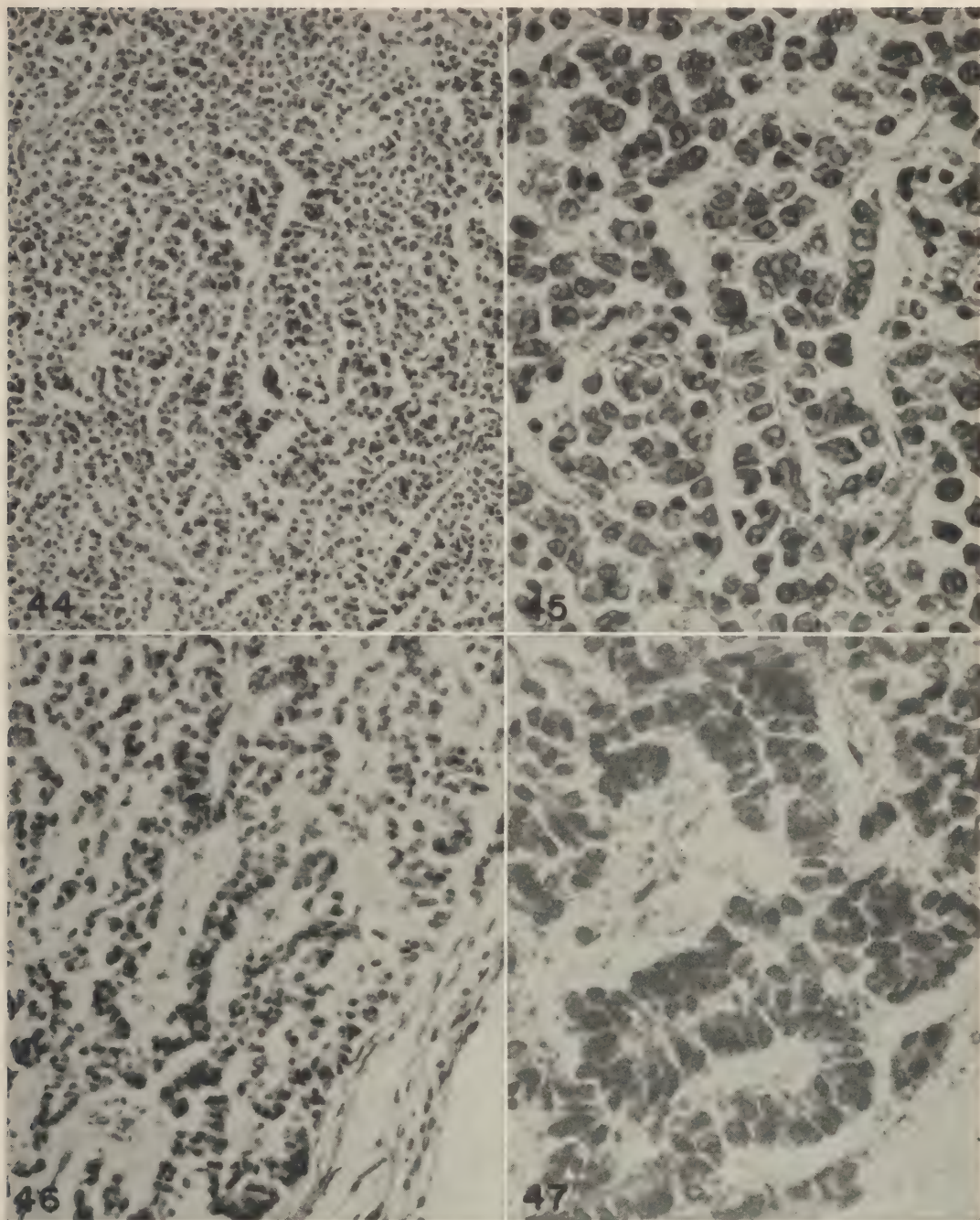


FIG. 44. Ependymoma forming indistinct canals. $\times 230$. AIP Neg. 96163.

FIG. 45. Ependymoma in higher magnification showing the distinct nucleus with scanty cytoplasm. $\times 650$. AIP Neg. 96179.

FIG. 46. Ependymoma with an orderly arrangement of cells on a reticulum background. $\times 230$. AIP Neg. 96182.

FIG. 47. Ependymoma with elongated cells forming canals and columns. $\times 500$. AIP Neg. 96150.

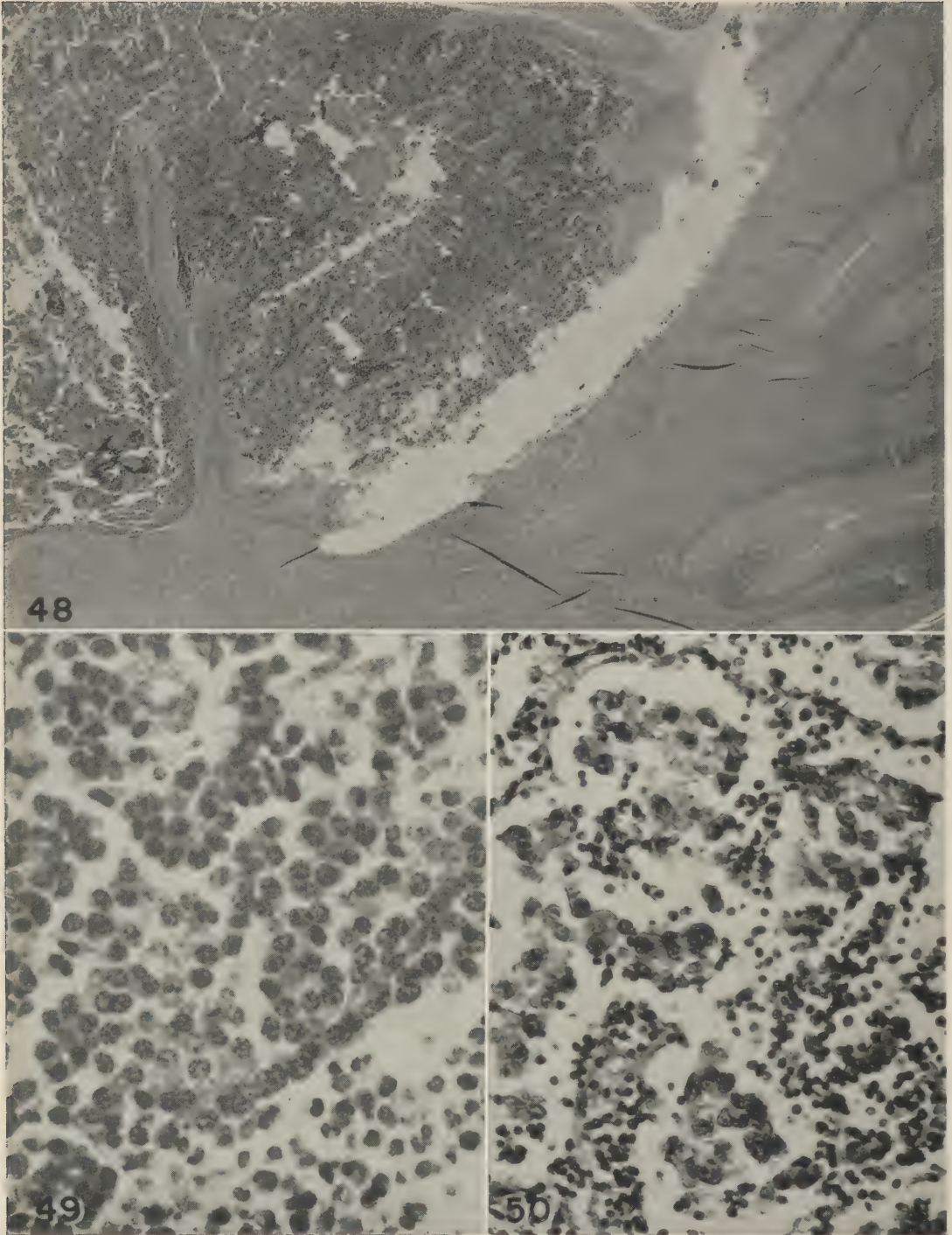


FIG. 48. Pinealoma invading the cerebellum. $\times 12$. AIP Neg. 96164.

FIG. 49. Pinealoma showing two cell types; larger cells with granular nuclei and smaller lymphocyte-like cells. $\times 450$. AIP Neg. 96165.

FIG. 50. Pinealoma with small clusters of large cells with distinct cytoplasm and small cells appearing as naked nuclei. $\times 330$. AIP Neg. 81380.

months, 5 months, 6 months, and 9 months. In one case the duration was 1 month, in another a year and a half, and in a third 2 years. No information as to duration was available in 3. History of trauma was recorded in one case.

The presenting symptoms of ependymoma were as variable as for other intracranial tumors. Headache was the most prominent in 10 cases, vomiting was a symptom in 6, nausea in 4, blurring of vision in 4, ataxia in 3, vertigo, diplopia and photophobia in 2 each. Other symptoms were: sudden onset of unconsciousness or coma, tinnitus, loss of vision, explosive speech, attacks of syncope, blindness, loss of libido, and personality changes.

Roentgenologic examination showed erosion of the sella turcica in 5 cases and calcification in one tumor.

Acute dysentery, generalized tuberculosis, and acute pyelonephritis were the causes of death in 3 cases in which ependymomas were incidental findings.

Craniotomy was performed in 9 cases. The postoperative deaths occurred in from 1 to 8 days. In one case in which no operation was performed sudden death followed spinal puncture.

Eleven of the 14 tumors were recognized clinically and the area of involvement was properly localized in 8.

Eight of the ependymomas were classified as epithelial, 5 as cellular, and the remaining as papillary.

Ependyoblastoma: One ependyoblastoma was found in a white male 22 years of age. The symptoms of nausea, vomiting, headache, and dizziness had been present for three months. Sudden coma occurred 1 day prior to operation. At craniotomy a tumor in the 4th ventricle was found to block the 3rd ventricle. No follow-up report is available.

Pinealoma (Pinealoblastoma and teratoma): Thirteen of the tumors were classified as pinealomas, representing 2.9 per cent of the entire series and 4.7 per cent of gliomas. All were in males, 12 white and 1 Negro, with an average age of 25.4 years.

Grossly, these tumors are well encapsulated,

often cystic, and frequently calcified. The external surface is usually smooth and lobulated. The tumors are soft, friable, and yellow-gray. The cystic spaces are filled with colloid-like material. Invasion of surrounding brain is common (Fig. 51).

Microscopically two types of cells predominate: (a) Large cells with abundant granular cytoplasm and prominent vesicular nuclei, containing 1 or 2 nucleoli, are arranged in sheets or round masses. The large cells are surrounded by small lymphocyte-like elements, and all are enmeshed in dense connective tissue. The larger cells resemble the cells of the adult pineal parenchyma and are supported by fine connective tissue stroma. (b) The other characteristic cells are small and round. (Fig. 49-56). They are particularly prominent in the more immature tumors.

Courville⁶ divides pinealomas into pineoblastomas, pinealomas, ganglioneuromas, teratomas and pineal cysts. Nine of the 13 tumors in this series were regarded as pinealomas. Of the remaining 4, 2 were pineoblastoma, and the other 2, teratomas of the pineal gland (Fig. 59-63).

The tumors, as the name implies, are located in the region of the pineal body. Ten in our series were close to the pineal gland. The major portion of the tumor was in the 3rd ventricle in two cases; in another the tumor appeared to be chiefly in the roof of the 4th ventricle (Fig. 48).

The duration of the disease from onset to diagnosis varied from 3 weeks to 1 year.

Duration

Less than 1 month	2
1-5 months	5
7-12 months	4
Unknown	2

The presenting symptoms and signs were headache in 8, papilledema in 7, blurring of vision in 4, weakness, deafness, diplopia, ataxia, and tinnitus in 3 each, nausea and vomiting in 2, polyuria in 1, and polydipsia in 1. Convulsions, lethargy, vertigo, hemiparesis, hemiplegia, optic atrophy, and nystagmus developed later but were not initial symptoms.

In our group pinealomas have extended as

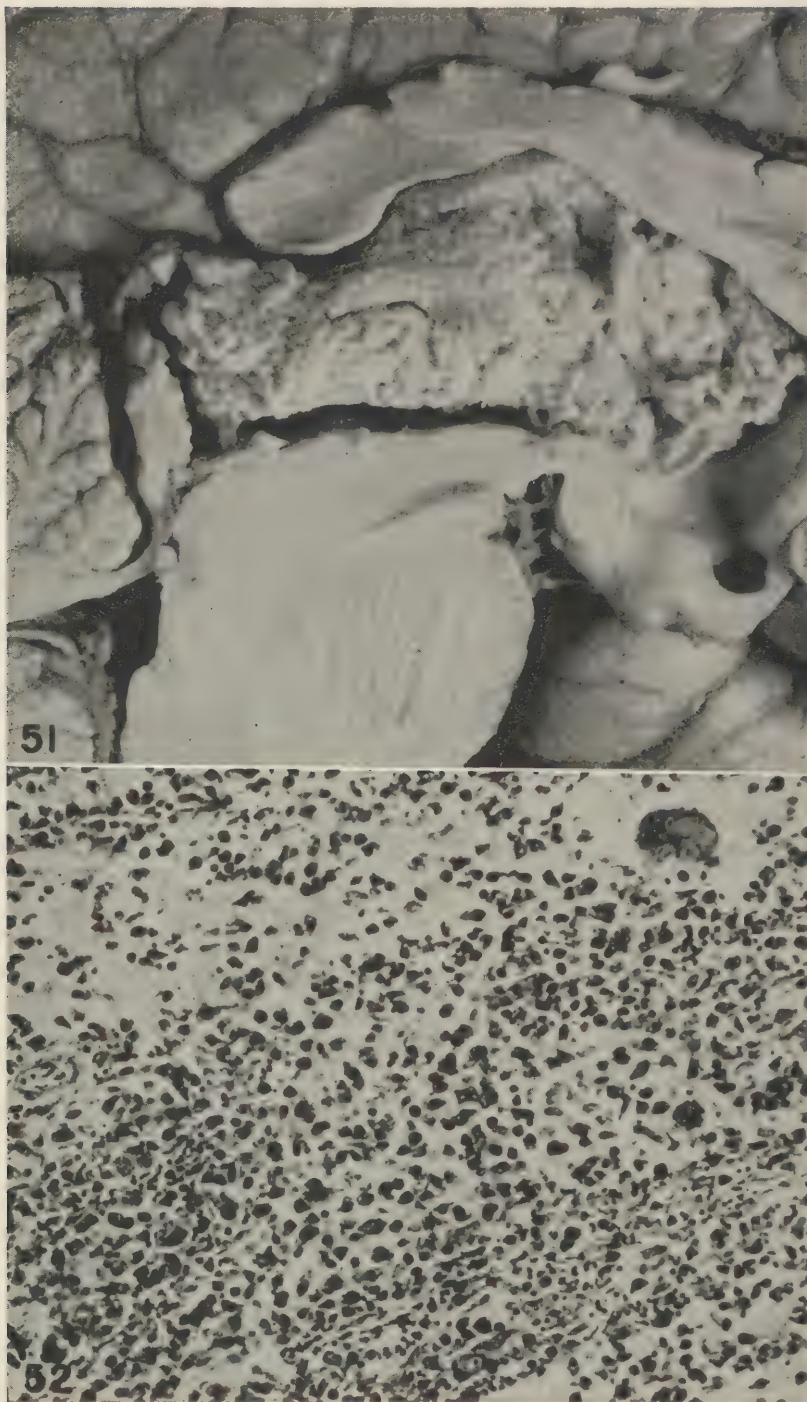


FIG. 51. Pinealoma filling the 3rd ventricle and extending into lateral ventricle. AIP Neg. 89297.

FIG. 52. Microscopic of the same pinealoma seen in (51). Note the two types of cells with an occasional giant cell. $\times 141$. AIP Neg. 93119.

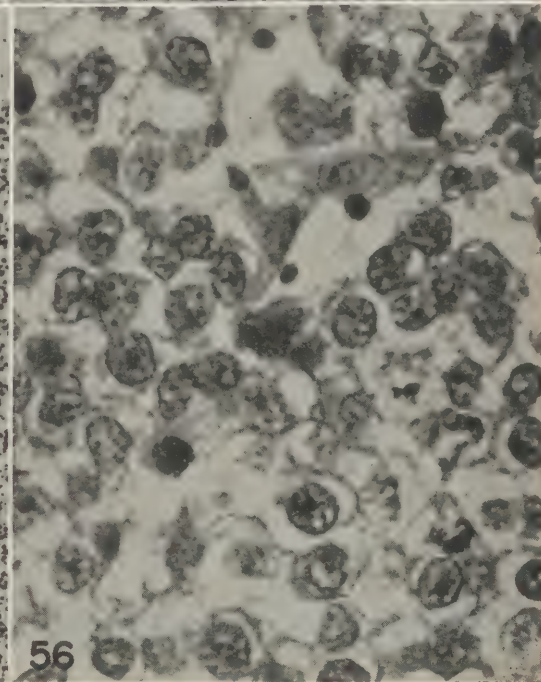
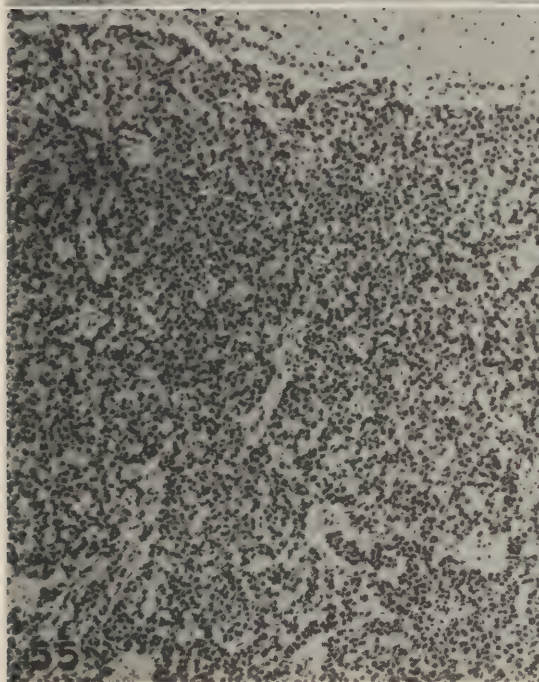
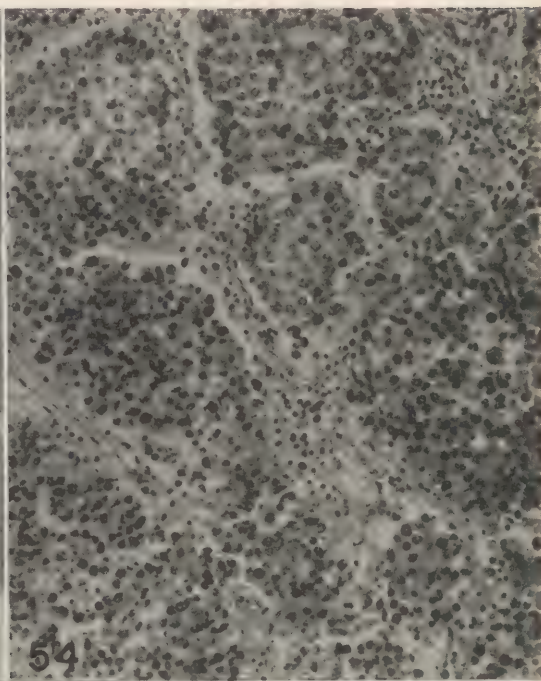


FIG. 53. Pinealoma with extension into pia arachnoid. $\times 7$. AIP Neg. 93549.

FIG. 54. Pinealoma showing two types of cells. Note the similarity to seminoma of the testes. $\times 210$. AIP Neg. 96164.

FIG. 55. Microscopic of pinealoma invading the pia arachnoid. Note the predominance of small cells. $\times 203$. AIP Neg. 93490.

FIG. 56. Pinealoma composed chiefly of large cells which resemble the cells of the adult pineal. $\times 700$. AIP Neg. 93494.

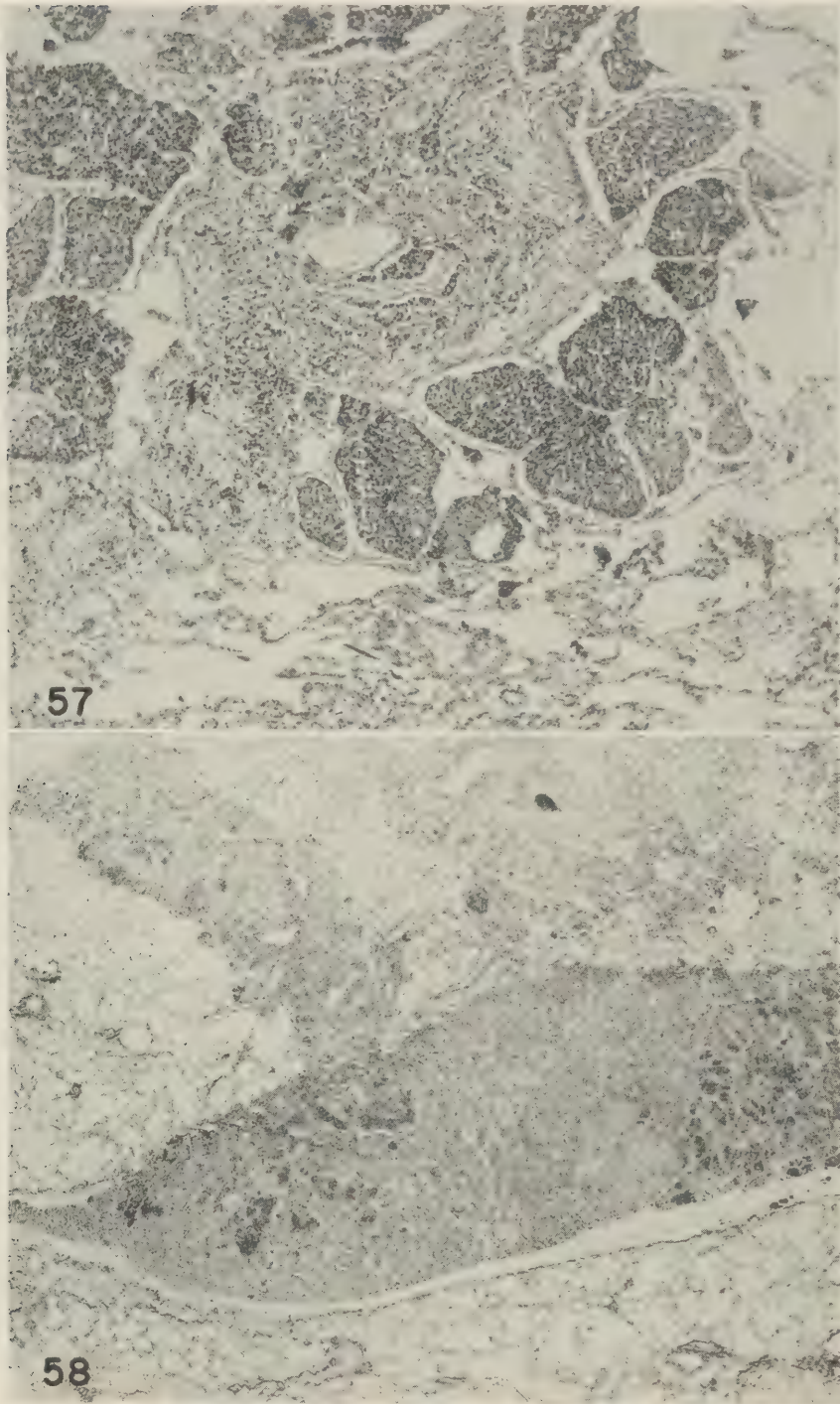


FIG. 57. Same as Fig. 55. Metastasis to the lung with primary tumor in the pineal gland. $\times 85$. AIP Neg. 93538.

FIG. 58. Metastasis to the lung from a pinealoma. $\times 85$. AIP Neg. 95307.

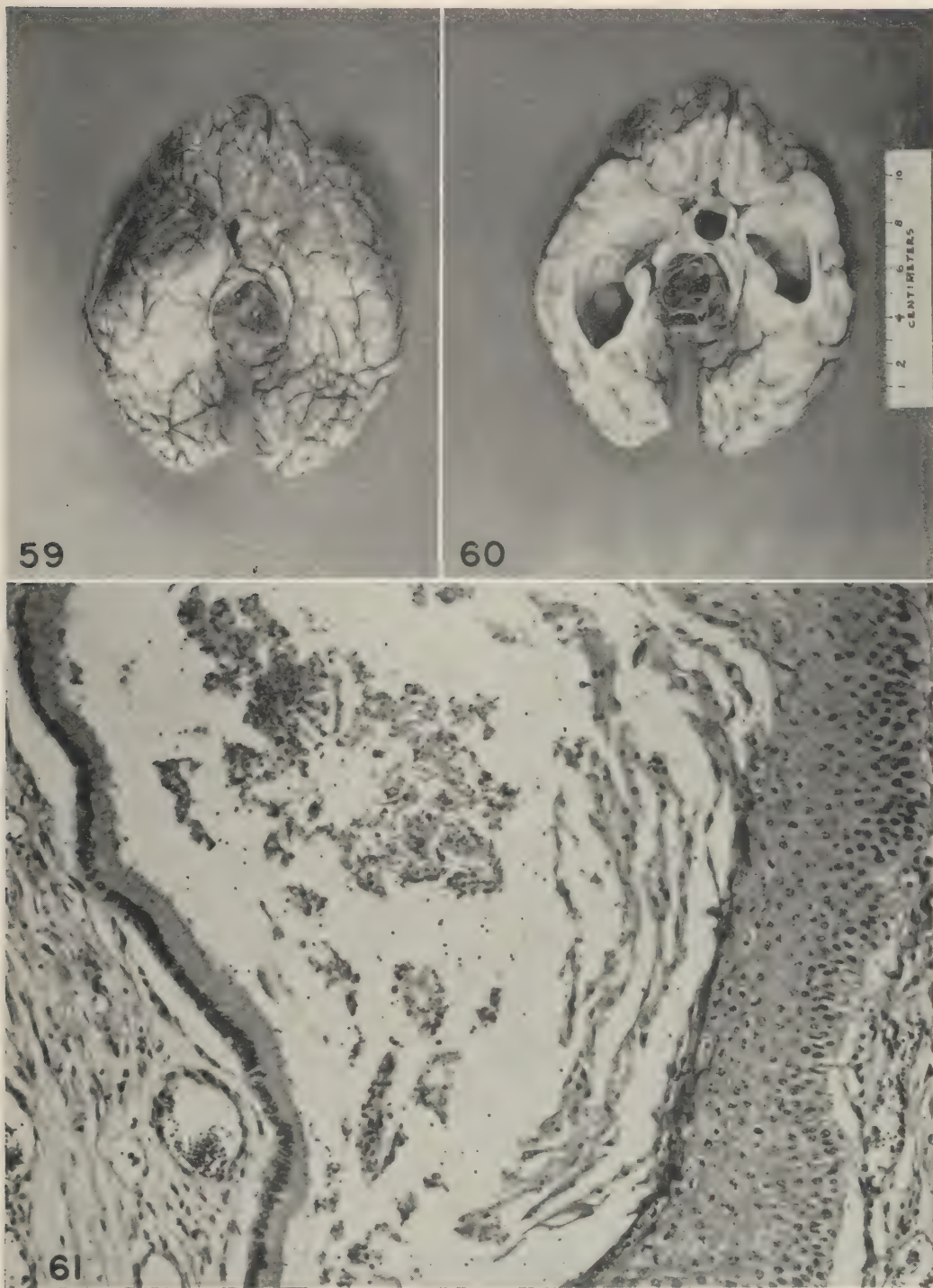


FIG. 59. Teratoma of pineal distorting the 3rd ventricle. AIP Neg. Bu 8386.

FIG. 60. Cross section of teratoma showing cystic cavities. AIP Neg. Bu 8386.

Fig. 61. Wall of one of the cystic spaces of the teratoma showing tall columnar epithelium and foci of stratified squamous epithelium. $\times 500$. AIP Neg. Bu 10-410.

far as the following structures: midbrain, thalamus, cerebral peduncles, cerebellum, aqueduct, 3rd ventricle and 4th ventricle. One teratoma of the pineal gland metastasized to the lung. It furnishes the only example of metastasis from an intracranial neoplasm in the entire series (Fig. 57 and 58).

Craniotomy was performed in 11 of the 13 cases. A diagnosis of pineal tumor was made from roentgenograms after a ventriculogram in 12 instances. Postoperative irradiation was given to one patient. Deaths occurred from 2 days to 11 months postoperatively. One death occurred 6 months after ventriculogram and in the absence of other surgery. One patient died suddenly while undergoing observation.

The period of survival after operation was as follows:

	Number	Per Cent
Less than 1 week	7	63.6
1-3 weeks	0	0
1-5 months	2	18.2
6-12 months	2	18.2
	—	—
	11	100.0

A diagnosis of pinealoma was made in 5 cases. The diagnoses of pituitary tumor, sub-arachnoid hemorrhage, intracranial neoplasm, psychosis, and brain tumor were made in the remainder.

Ganglioneuroma (Ganglioglioma): Six intracranial tumors were classified as ganglioneuroma. This represents 1.3 per cent of the series, and 2.2 per cent of gliomas. All the patients were white, 5 were men and 1 a woman; the average age was 26.1 years.

The gross appearance of ganglioneuroma is not distinctive. The tumor is usually rather diffuse and appears as a firm, gelatinous, slightly elevated mass in the brain substance, with little or no line of demarcation. Occasionally cysts and hemorrhages are seen.

The term ganglioneuroma implies that nerve cells or ganglion cells are neoplastic and active components of a glioma. The difficulty in making the diagnosis lies in differentiating neoplastic nerve cells from preexisting nerve cells incorporated in other varieties of tumor. Usually, however, one sees scattered through

the astrocytic elements of the tumor large, often multinucleated ganglion cells with vesicular nuclei and prominent nucleoli. The cytoplasm is basophilic, vacuolated, and contains Nissl's granules. These large cells are usually surrounded by satellites, and lie in a matrix of nerve cell processes and glial fibrils (Fig. 64-68). The nerve elements (neurocytes), generally show various stages of degeneration. Kuhlénbeck and Haymaker¹⁵ have classified these tumors according to the terminology of Globus as spongioneuroblastomas and glioneuromas depending on the degree of maturity of the cells involved. Some of the nerve cells are hyalinized, or the Nissl substance appears to be clumped (Fig. 69). Neuronophagia is not uncommon.

Ganglioneuromas are usually located in the cerebral cortex. In our group one arose in the left parietal region and extended into the thalamus and corpus callosum. Another had its origin in the pineal region between the superior and inferior colliculus and invaded the pons and cerebellum. One tumor, arising in the basal ganglia, extended into the sella turcica. One was in the pontine region, another in the right thalamus, and the sixth arose in the vicinity of the optic tract and chiasm.

The duration from onset of symptoms to diagnosis varied. Two patients had symptoms for 1 month, one for 5 months, another for two and a half years; 2 tumors apparently were symptomless and were incidental findings at post mortem.

Again headache was the most common symptom, and was present in 4 cases, blurred vision in 2, vomiting, loss of vision to blindness, hypalgesia of the finger, hemiparesis, papilledema, diplopia, and vertigo in 1 each.

A preoperative roentgenogram showed calcification in the region of the sella turcica in one case.

Craniotomies were performed on 3 patients. One died 2 days and one 4 months following craniotomy, the fate of the third is unknown. Two other deaths unrelated to brain tumor were caused by septicemia and gunshot wound of the abdomen.

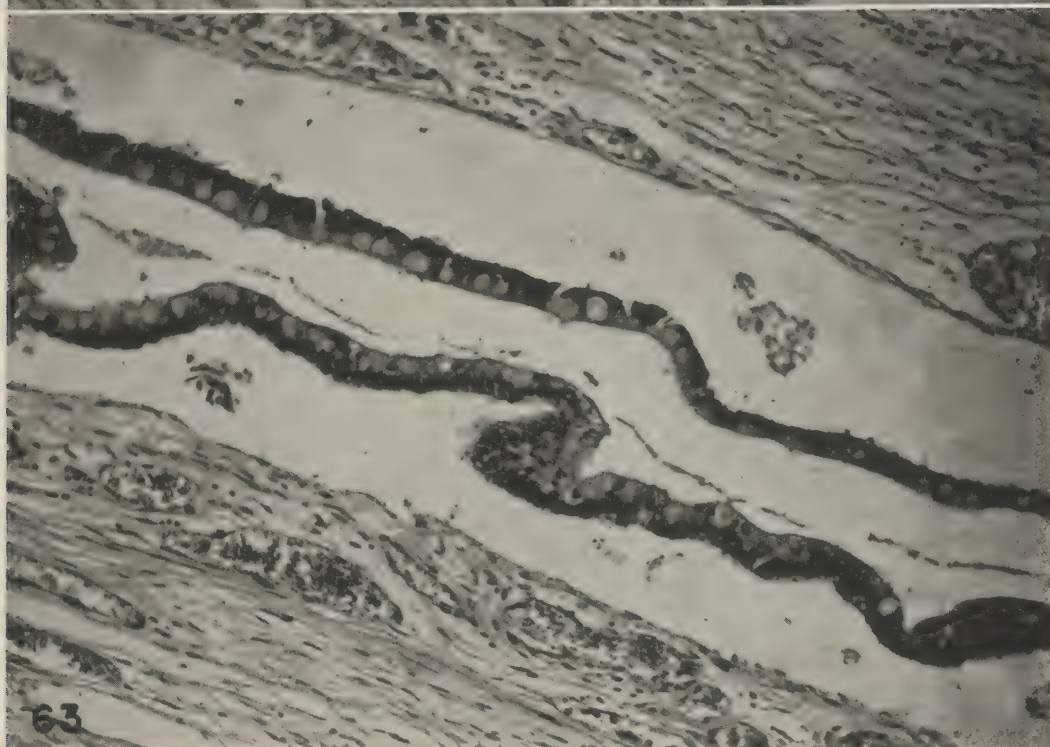
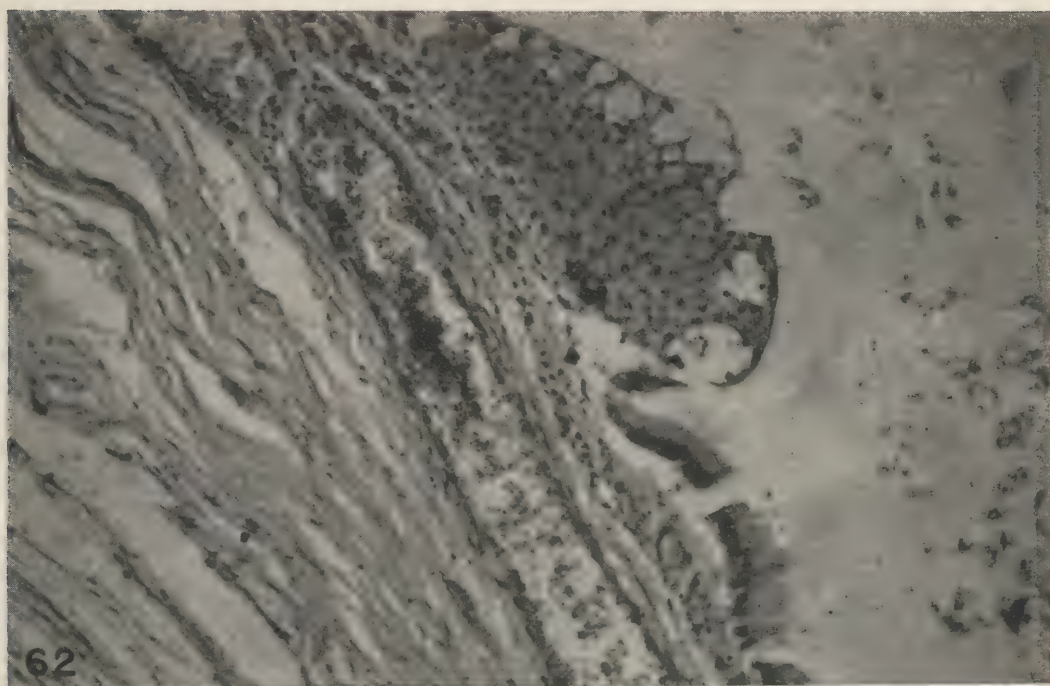


FIG. 62. Columnar epithelium of wall with foci of stratified squamous epithelium. AIP Neg. Bu 10-413.

FIG. 63. Another area of teratoma of pineal gland showing goblet cells and vascular connective tissue base. $\times 500$. AIP Neg. Bu 10-410.

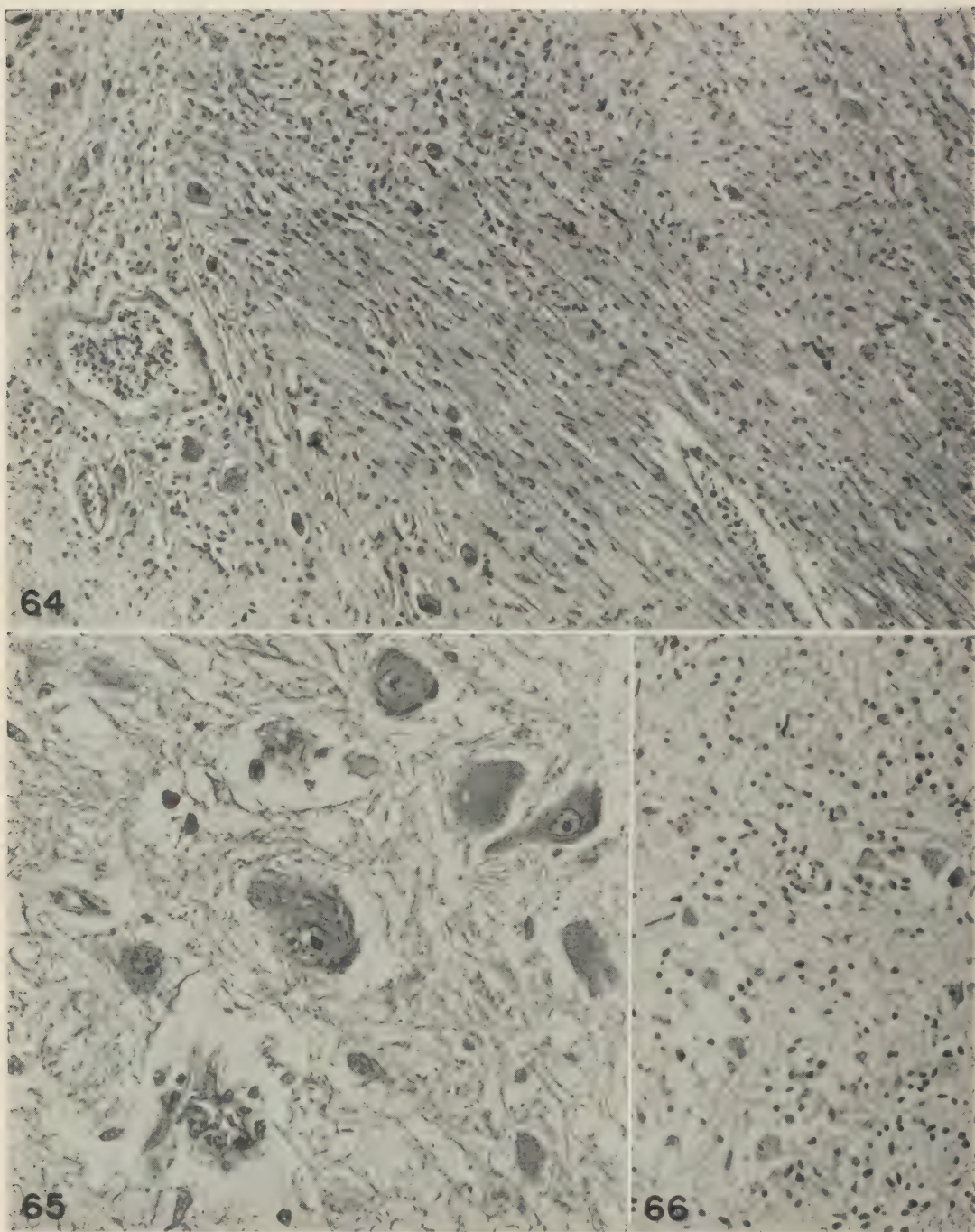


FIG. 64. Ganglioneuroma showing spongioblasts and nerve cells. $\times 160$. AIP Neg. 95383.

FIG. 65. A higher magnification of the proliferating nerve cells in a ganglioneuroma. Note the distinct nucleolus and Nissl's granules in the cells. $\times 450$. AIP Neg. 95371.

FIG. 66. Ganglioneuroma or spongioneuroblastoma; neoplastic glial elements and proliferating nerve cells. $\times 175$. AIP Neg. 95387.

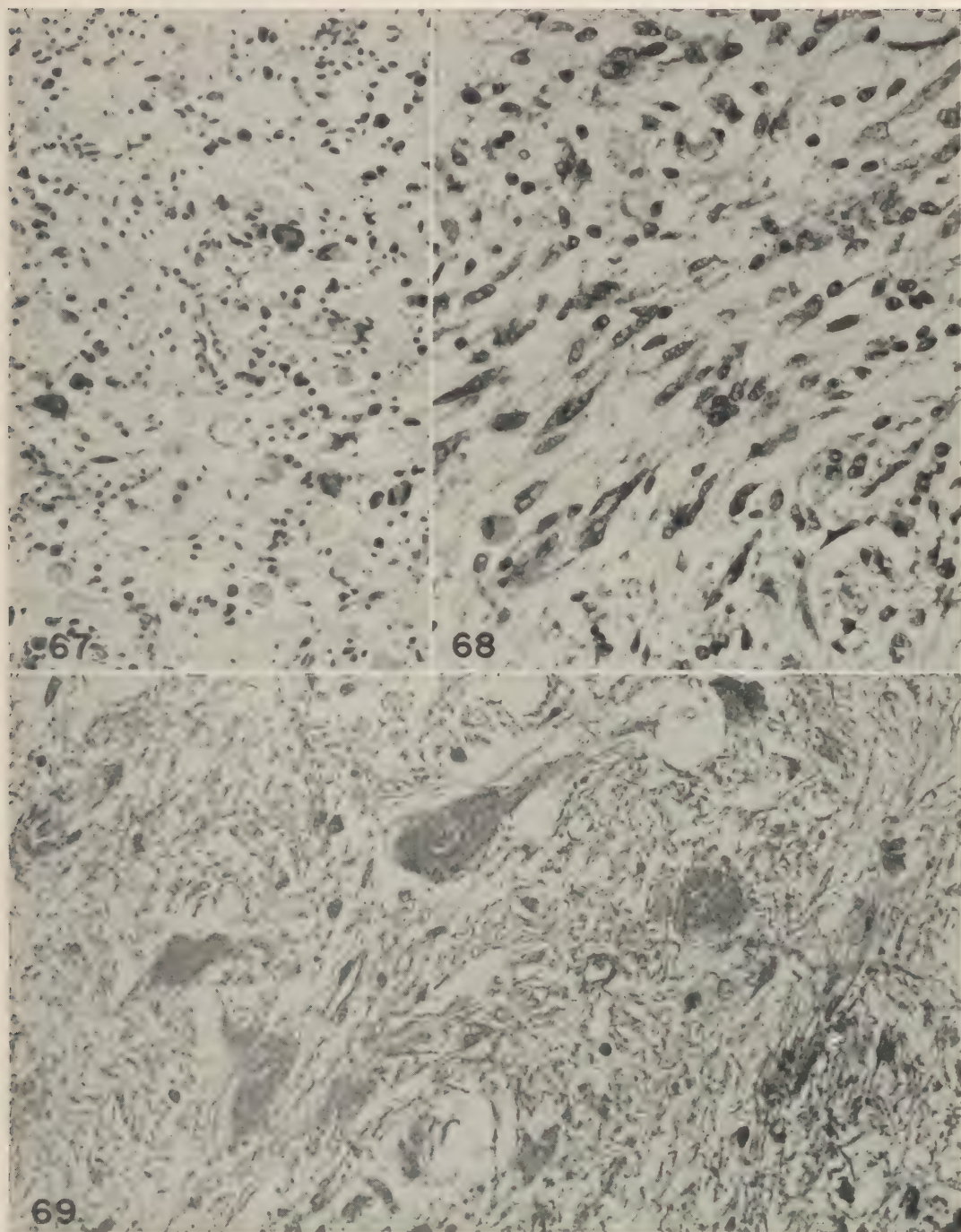


FIG. 67. A focus of glioblastoma multiforme in a ganglioneuroma. A mixed variety of tumor. $\times 175$. AIP Neg. 95389.

FIG. 68. A focus of spongioblastoma polare in a ganglioneuroma (spongioneuroblastoma). This tumor contained 4 different glial patterns. $\times 400$. AIP Neg. 95404.

FIG. 69. Proliferating nerve cells in a ganglioneuroma. $\times 550$. AIP Neg. 95369.

Brain tumor was diagnosed in 3 of the 4 cases with symptoms and in the other a diagnosis of acute disseminated sclerosis was made.

Neuroepithelioma: One neuroepithelioma was seen in the series, and an additional tumor, not included in the series, was observed in a patient 44 years of age. The patient was a 33-year-old white male who had had symptoms of headache and impaired vision in the right eye for 5 months. A ventriculogram was followed by craniotomy, revealing a tumor in the region of the sella turcica which could not be removed. The diagnosis of neuroepithelioma was made on examination of the tissue removed at operation.

This rare tumor is formed by cells which arise directly from neuroepithelium and which resemble primitive spongioblasts. The gross appearance is not characteristic. The tumor may be located anywhere in the cerebrum. While it is uncommon in the central nervous system, it occurs more frequently in the retina and spinal cord. The microscopic picture resembles that of the primitive neural tube or of glioma of the retina. The primitive elongated cells are arranged in rosettes, with the central space surrounded by cells which appear to radiate from it. There is a definite internal limiting membrane. The inner lining of the cells is often ciliated and contains small granular bodies, so-called "blepharoplasts." The rosettes are separated by cuboidal or columnar cells which are arranged in bands and columns resembling medulloblasts. Mitotic figures are common. Neuroepitheliomas on occasion metastasize out of the central nervous system.

Atypical Malignant Glioma (Unclassified): Only 3 "malignant gliomas" were found among the 446 intracranial neoplasms. They made up 0.7 per cent of all tumors and 1.1 per cent of gliomas studied. All occurred in males, 2 white and 1 Negro; the average age was 28.6 years.

The gross appearance of so-called malignant gliomas may simulate that of any other intracranial tumor, but they do not conform to any morphologic type, and hence are usually designated as unclassified gliomas. The

malignant gliomas are believed to be atypical or transitional forms of other kinds of gliomas.

Microscopically, the cells are usually spindle shaped and resemble neuroblasts. The picture varies from solid masses of lymphoid-like cells with scanty cytoplasm to multinucleated cells similar to those seen in glioblastoma multiforme.

The location of one tumor was not given, another was in the medulla and the third in the left frontal lobe with extension into the temporal lobe.

One patient had been operated on 6 years before. A craniotomy was performed on one who later received irradiation. One patient died during insulin shock treatment for battle fatigue.

Symptoms were present for 1 month in 1 case, and for 1 year in 2 cases. The symptoms at the time of diagnosis were vomiting, stupor, hemalgesia, nystagmus, convulsions, and periodic unconsciousness.

The diagnosis of brain tumor was made in two cases and the other was called bulbar encephalitis. No history of trauma was recorded.

PITUITARY ADENOMA

Twenty-six (5.8 per cent) of the intracranial neoplasms were classified as pituitary tumors. The group is divided into: (1) chromophobic adenomas representing 22 or 4.9 per cent, of all intracranial tumors, (2) eosinophilic adenomas, 3, or 0.7 per cent, and (3) malignant adenomas, 1, or 0.2 per cent.

Only tumors which produced characteristic symptoms were included in this study; lesions which were incidental findings were omitted, except for 2 eosinophilic adenomas. In 1 case of Cushing's syndrome, pituitary basophilism was noted, but no definite adenoma was found.

Chromophobe Adenoma: Twenty-two tumors, or 4.9 per cent, proved to be chromophobe adenomas; 20 were in males and 2 in females; 16 in whites, 4 in Negroes and 1 in an Hawaiian. The average age of the patients was 28.4 years.

All the tumors were found in the sella turcica. Two of the larger had compressed the

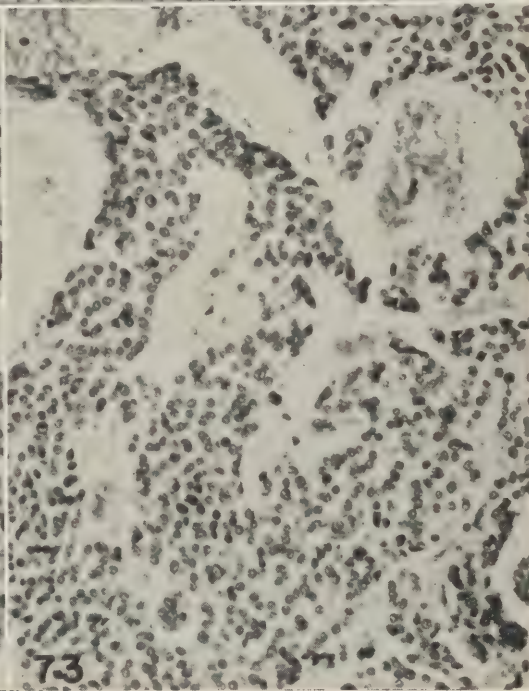
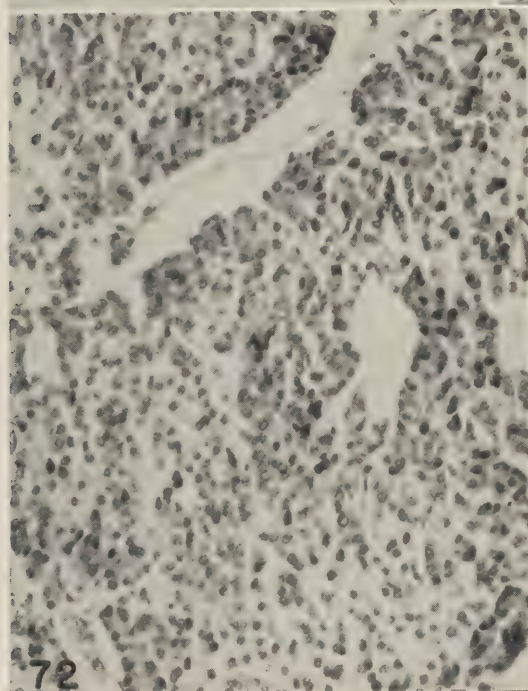
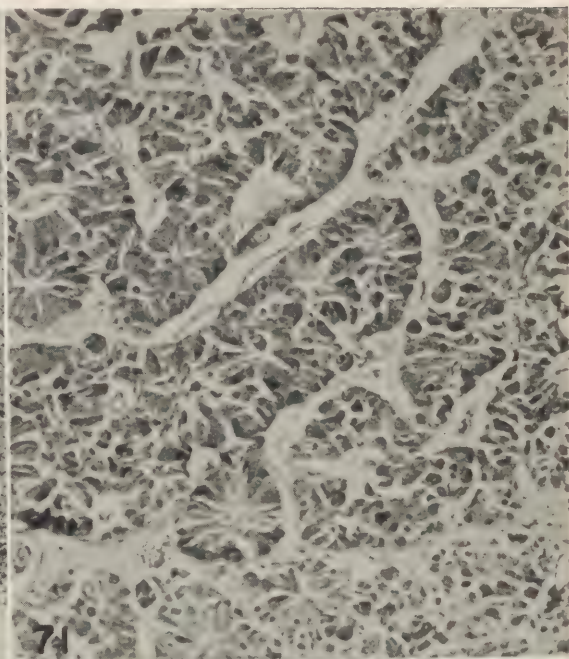
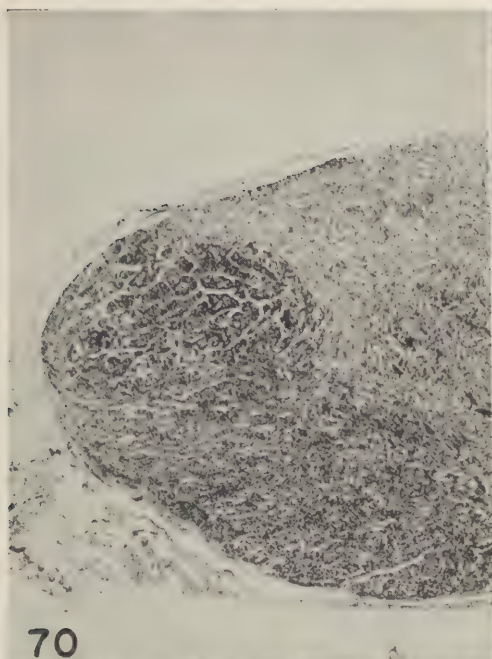


FIG. 70. Chromophobe adenoma of the pituitary. AIP Neg. 82224.

FIG. 71. Chromophobe adenoma of pituitary. Note the adenomatous arrangement of the cells. AIP Neg. 85226.

FIG. 72. Chromophobe adenoma of the pituitary. AIP Neg. 96180.

FIG. 73. Chromophobe adenoma of pituitary. AIP Neg. 96166.

pons, 11 had compressed the optic chiasm, giving rise to visual symptoms, without invasion of the surrounding structures. Grossly, chromophobe adenomas are soft, globoid and encapsulated; they vary from 3 mm. to 2.5 cm. in diameter. The cut surface is red-gray and often cystic. They cannot be distinguished grossly from eosinophilic adenomas.

The cells are pale, roughly round to polygonal in shape, with an abundant finely granular cytoplasm which does not stain well. Fine mitochondria may be seen. The nuclei are oval and deeply basophilic. The cells are divided into clumps or islands by vascular connective tissue strands. (Fig. 70-73).

Pituitary dystrophy, infantilism, and Froehlich's syndrome are a few of the endocrinologic features of these tumors. Other signs and symptoms are related to the location of the tumor or to increased intracranial pressure.

The duration of symptoms from onset to diagnosis are as follows:

Time	Number	Per Cent
Less than 1 month	2	9.1
2-5 months	5	22.7
7-11 months	5	22.8
1-2 years	6	27.2
Over 2 years	2	9.1
Unknown	2	9.1
	—	—
	22	100.0

The symptoms were predominantly visual, as evidenced by failing or blurred vision, complete blindness, bitemporal hemianopsia and homonymous hemianopsia. Other symptoms related to pituitary dysfunction were absence of body hair, obesity, acromegaly, polyuria, dwarfism and female contours. The remaining symptoms resulted from intracranial pressure. Trauma was suggested as a predisposing factor in 2 cases.

Preoperative roentgenograms showed enlarged or eroded sella turcicas in 14 patients.

Craniotomy was performed in 18 cases; postoperative death occurred in 7; on the day of operation in 1 case, 1 day after operation in 3, 2 days after operation in 2, and 4 days after operation in 1.

The clinical diagnoses were as follows:

Pituitary tumor	20
Rathke pouch tumor	1
Encephalitis	1

Eosinophilic Adenoma: Three of the pituitary tumors were classified as eosinophilic adenomas. Two were in white males and 1 in a Negro male; the ages were 22, 23 and 25 years.

Two of the 3 patients had had acromegaly for 3 and 7 years respectively. Optic atrophy was demonstrated by ophthalmoscopic examination, and one patient had been totally blind for a year. Roentgenograms showed an enlarged sella turcica in 2 patients. The third patient had been without vision in the left eye for 3 months, was obese, and had female distribution of hair.

Operation was performed in all 3 cases; 2 of the tumors removed were eosinophilic adenomas while the third was mixed, with eosinophilic cells predominating. There were no postoperative deaths.

The histologic picture shows oval to polygonal cells with a moderate amount of cytoplasm containing numerous fine eosinophilic granules. The cells were arranged in sheets or alveoli, and suspended on a thin scanty vascular stroma. The fine eosinophilic granules are called the "alpha" granules. The eosinophil cells are often mixed with chromophobe elements.

Malignant Adenoma (Adenocarcinoma of Pituitary): One case was diagnosed as malignant adenoma. The tumor occurred in a white male of unknown age. The symptom was progressive loss of vision for 1 year. Enlargement of the sella turcica was seen in the preoperative roentgenogram. Craniotomy was performed. The microscopic picture showed features of chromophobe adenoma with marked hyperchromatism and numerous mitotic figures.

MENINGIOMA

Thirty-nine tumors in the series were classified as meningiomas; that is, as dural endotheliomas, meningeal fibroblastomas, leptomeningiomas, and arachnoidal meningeal fibroblastomas. These make up 8.7 per cent of

this series. Thirty-four occurred in males and 4 in females; 36 patients were white and 2 colored. In the period from Pearl Harbor to V-J day, 17 additional meningiomas were seen in patients over 38 years of age. The majority (10) of these were in the fifth decade. The average age of the patients was 28.4 years, and that of the group including the older patients was 38.8 years.

The meningiomas are gray to reddish brown, well encapsulated, nodular tumors. A majority of them at some point are attached to the dura. They are usually very vascular and commonly contain foci of calcification. Meningiomas may invade bone and brain substance, but more often compress the surrounding structures (Fig. 74). A reactive exostosis of the cranium is sometimes associated. These tumors may arise from the leptomeninges anywhere in the calvarium, frequently in the midline along the parasagittal region. Meningiomas spreading over surface of the brain are referred to as endotheliomas or meningiomas "en plaque." The cut surface is often gritty because of the calcified particles (psammoma bodies) or spicules of bone.

The meningiomas are classified as angio-blastic, chondroblastic, osteogenic, fibromatous, and sarcomatous on the basis of predominating morphologic features (Fig. 75-81).

Bailey and Bucy⁸ have a classification based on the family resemblance and histofunctional differentiation of cells. They designate a *fibroblastic* variety, characterized by sheets of proliferating fibroblasts with no whorl formation in which the vessels are usually large and often hyalinized. The *meningotheiomatic* variety is made up of sheets of cells with large vesicular nuclei and plentiful granular cytoplasm. The masses of cells are separated into lobules by vascular connective tissue strands. Hyalinized fibrils are common. The *psammomatous* variety tends to form whorls composed of rather plump cells. The whorl may consist of a compact nest of cells only or it may be arranged around a central blood vessel. The center often contains calcified masses, the

so-called psammoma bodies. The *mesenchymal* variety is distinguished by a type of cell which shows more apparent activity which is reflected in the rather rapid growth. The distinctive cells are bipolar or stellate with large interlacing cytoplasmic processes. The numerous vessels of the tumor are thin walled. Myxomatous degeneration is often seen. The *angioblastic* variety is distinguished by marked cellularity. The cells are arranged in irregular sheets, with giant cells scattered throughout. Small and large irregular endothelial lined spaces separate the islands of cells. The background of the tumor is a fine reticulum network. The *melanoblastic* variety is made up of the chromatophores of the leptomeninges and is characterized by long spindle shaped cells which accumulate around vessels and may or may not contain pigment. Mitoses are common. The growth of the tumor is rapid and progressive. The *sarcomatous* variety is usually a diffuse tumor composed of large oval and round cells with eosinophilic cytoplasm and eccentrically placed, hyperchromatic nuclei. The arrangement of cells around vessels has caused the tumor to be referred to as perithelial or perivascular sarcoma. Mitoses are common (Fig. 81). The *lipomatous* variety is usually seen on the dorsal surface of corpus callosum or in the region of tuber cinereum, mammillary bodies, or midbrain. The cells are mature fat cells with varying degrees of interstitial connective tissue. The *osteochondroblastic* variety is composed chiefly of mature bone and cartilage with islands of cellular connective tissue and fat (Fig. 78).

The majority of meningiomas consist of plump fusiform cells with vesicular nuclei. The cells are arranged in whorls and sheets with or without calcium granules. The predominating cell is mesenchymal in origin.

The classification of meningiomas in this series is as follows:

Meningioma (without qualifying classification)	15
Osteogenic	2
Psammomatous	4
Fibroblastic	8
Fibrous	1

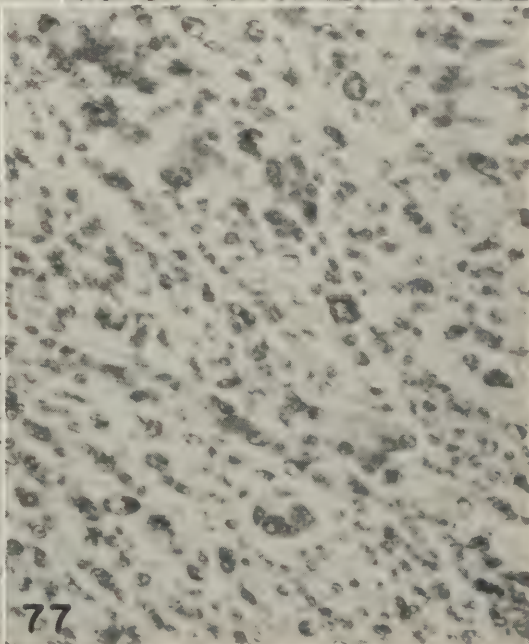
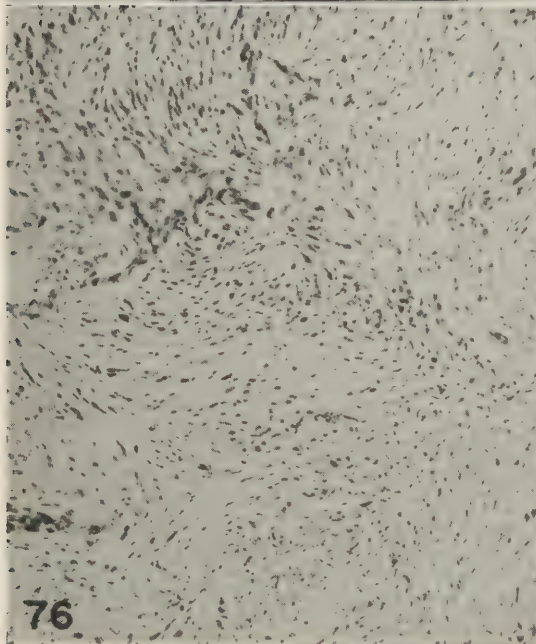
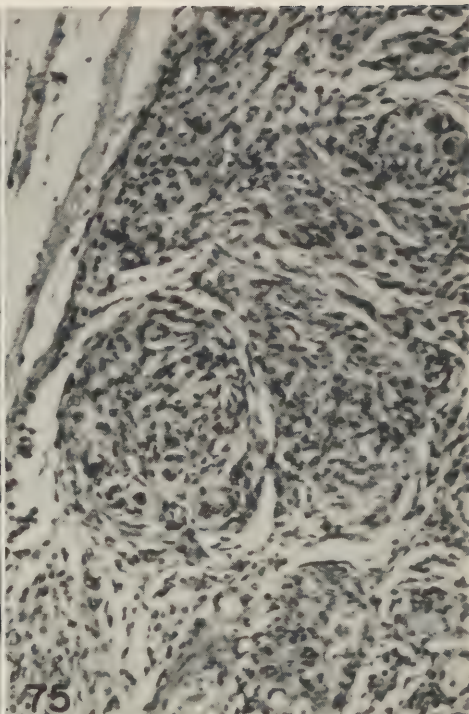
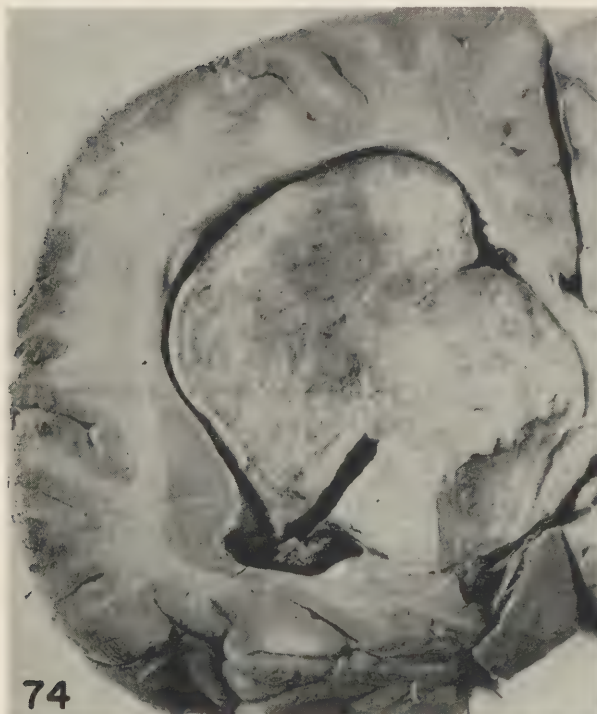


FIG. 74. Meningioma arising in the lateral ventricle. AIP Neg. 80248.

FIG. 75. Cellular meningioma with characteristic whorls and strands of cells. $\times 175$. AIP Neg. 96263.

FIG. 76. Fibrous type of meningioma. $\times 90$. AIP Neg. 96251.

FIG. 77. Cellular meningioma with few tumor giant cells and multinucleated giant cells. $\times 230$. AIP Neg. 96252.

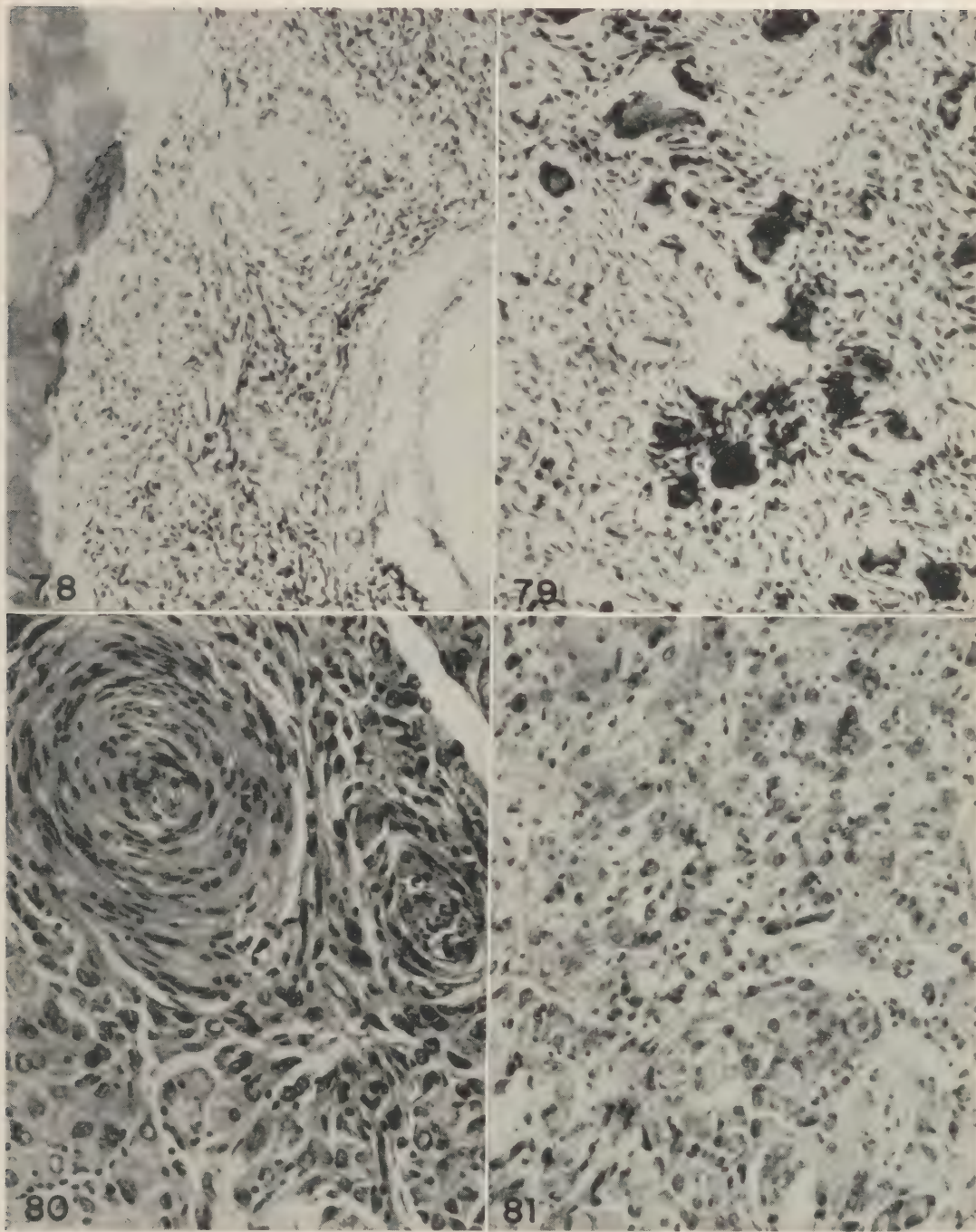


FIG. 78. A meningioma invading bone and forming islands of cartilage. AIP Neg. 96243.

FIG. 79. A meningioma with numerous calcified masses, some of which are spicules of bone, the osteoblastic variety. AIP Neg. 96256.

FIG. 80. A meningioma with atypical cells adjacent to the characteristic whorls. The atypical cells represent malignant change. AIP Neg. 96259.

FIG. 81. A malignant meningioma with atypical cells with hyperchromatic nuclei, some of which are giant forms. AIP Neg. 96170.

Meningothelial	1
Cellular	1
Angioblastic	2
Malignant	5

There is no correlation between the type of meningioma and the location of the lesion.

Location of meningiomas:

	Right	Midline	Left
Cerebellum	1	2	1
Frontal lobe	1	0	4
Parietal lobe	1	0	3
Temporal lobe	1	0	5
Occipital lobe	1	0	1
Sphenoid wedge	1	0	2
Parasagittal	0	8	0
Sella turcica	2		
Lateral ventricle	1		
3rd ventricle	1		
Multiple	1		
Unknown	2		
	—	—	—
Total:	13	10	16

Four meningiomas had extended into and invaded the bone; 4 others invaded the brain. Two tumors arising in the pia had extended into the dura. One of the meningiomas was associated with hyperostosis frontalis.

The duration from onset of symptoms to clinical diagnosis is as follows:

	Number	Per Cent
Less than 1 month	2	5.1
1-5 months	14	35.9
6-11 months	5	12.8
1-2 years	9	23.1
Over 2 years	4	10.3
Incidental	3	7.7
Unknown	2	5.1
	—	—
	39	100.0

A mass, present in the nose of one patient since birth, on removal was diagnosed as a cellular meningioma. Trauma was mentioned in 4 cases in which it preceded the onset of headaches.

Headache was again the most prominent symptom (in 23 cases) and other presenting symptoms and signs were papilledema in 15 cases, impaired vision in 7, facial weakness, diplopia, vomiting and vertigo in 5 each, loss of vision in 4, and Jacksonian convulsions in 4. Nystagmus, coma, hemiparesis, pain in the

neck, syncope, nausea, lethargy, generalized convulsion, and rectus palsies, each were observed in 3 cases. Ataxia, stiff neck, loss of smell, pain in the arm, and uncinat fits also were early symptoms.

The preoperative roentgenogram showed calcification in 5 tumors, erosion of the sella turcica in 2, and invasion of the calvarium in 3.

Craniotomy was performed in 32 cases and ventriculograms in 10. Seven patients died postoperatively, 1 on the day of operation, others 1, 2, and 8 days, and 1, 3, and 5 months later. Three patients died in coma before operation could be undertaken. The remaining 3 deaths were caused by carcinoma of the esophagus, subarachnoid hemorrhage, and an automobile accident.

Four cases had recurrences from 3 months to 2 years after the initial craniotomies. Three craniotomies were performed on one patient for recurrences in the same region.

A clinical diagnosis of brain tumor was made in 33 cases. Pituitary tumor, encephalopathy, subacute endocarditis, subarchnoid hemorrhage, meningocele (nasal), and carcinoma of esophagus were the diagnoses in the remaining cases.

NEUROFIBROMA

This group includes all tumors arising from cranial nerves: fifteen of these, or 3.4 per cent, are included in the series. All neurofibromas occurred in white males, with an average age of 26.0 years.

The tumor is nodular, well encapsulated, yellow-gray, and incorporates nerve structures. The usual location is in the region of the 8th nerve (acoustic) but any cranial nerve may be involved. Soft yellow areas of degeneration may be scattered throughout the firm gray tumor. Neurofibromas are often adherent to surrounding brain, meninges, vessels, cerebellum, and bone, but usually can be shelled out. The tumor is round or oval with the long axis of the mass parallel to the nerve. The internal acoustic meatus is often enlarged by extension of the tumor along the nerve (Fig. 82).

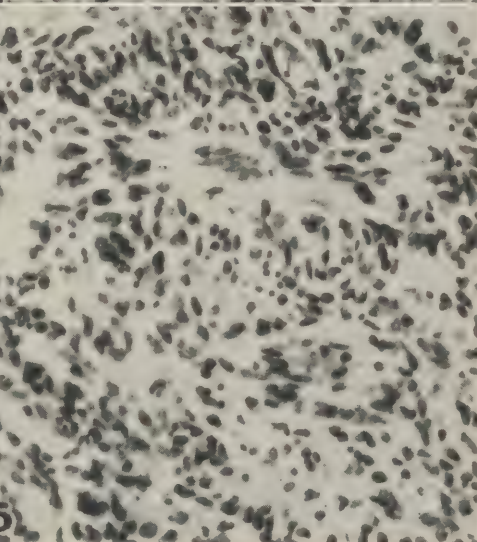
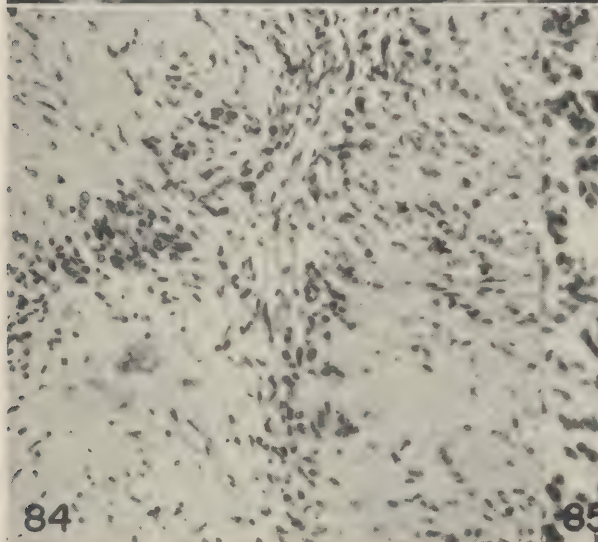
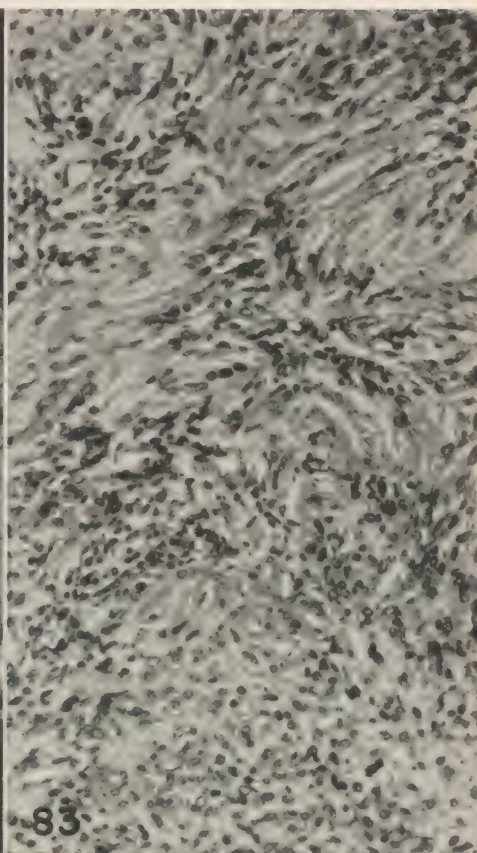
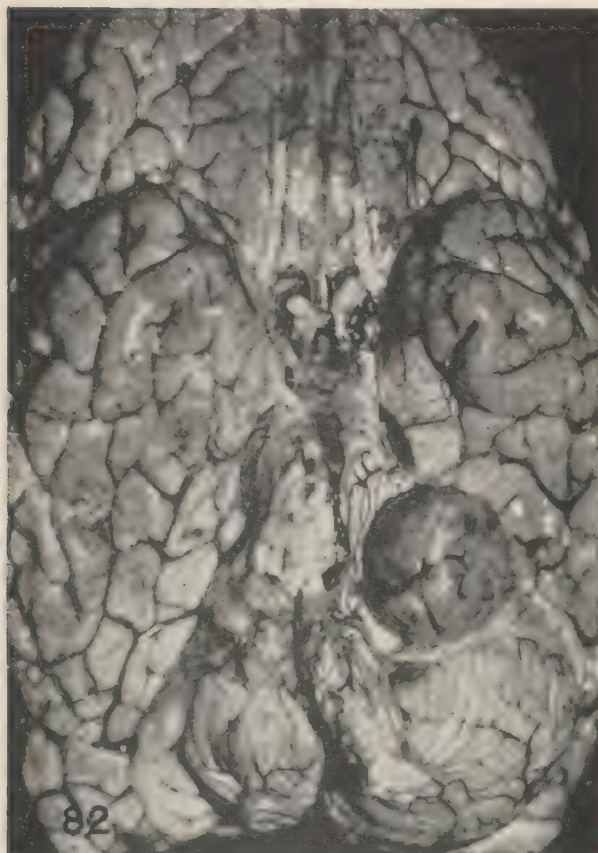


FIG. 82. A right acoustic neurofibroma. Note the shifting and compression of pons and brain stem. AIP Neg. 84991.

FIG. 83. A neurofibroma of the 8th nerve with characteristic palisading. $\times 250$. AIP Neg. 96173.

FIG. 84. A fibrous neurofibroma with palisading about a vascular connective tissue. $\times 200$. AIP Neg. 96188.

FIG. 85. A cellular neurofibroma with some attempt at palisading. $\times 230$. AIP Neg. 96159.

The predominating cell is elongated and spindle shaped with a vesicular nucleus. In places these cells tend to accumulate in a parallel fashion forming a palisade. Other cells are stellate with homogeneous vacuolated cytoplasm and relatively short fibrils. The processes formed by the cells are arranged in interlacing bundles and whorls. A few macrophages containing lipoid material are scattered throughout the tumors. The reticulum fibers are usually prominent. Mitoses are uncommon (Fig. 85).

In this series the acoustic nerve (8th) was involved in 14, the trigeminal (5th) in one. Seven of the neurofibromas were regarded as neuromas while 4 others were called perineural fibroblastomas.

The tumors were located as follows:

	<i>Right</i>	<i>Left</i>	<i>Bilateral</i>
Acoustic nerve	6	6	2
Trigeminal	0	1	0

Three tumors were features of von Recklinghausen's disease. Multiple intracranial neurofibromas were found in 1 case, and in 4 the tumor had extended into the petrous bone and involved a portion of the cerebellum.

The duration from the onset of symptoms to diagnosis was more prolonged with tumors of this type.

	<i>Number</i>	<i>Per Cent</i>
Less than 1 month	1	6.7
2-5 months	2	13.3
6-12 months	4	26.7
1-2 years	5	33.3
3-5 years	2	13.3
Over 5 years	1	6.7
	15	100.0

The presenting symptoms and signs were related to the nerve, to the side involved, and usually to the mechanisms of hearing and balance. Ataxia, tinnitus, headache, and deafness were most frequently encountered, other symptoms were papilledema, nystagmus, cafe au lait spots, dimness of vision, diplopia, vertigo, vomiting, failing hearing, nausea, blindness, lethargy and paralysis of the vocal cord. In one case the symptoms of headache and gradual progressive deafness had been present throughout life.

The preoperative roentgen examinations showed enlargement of the acoustic meatus in 3, and erosion of the petrous bone in 1 case. Fourteen of the 15 patients underwent operation, and one half are known to be alive. Postoperative death occurred in 7 cases. One patient died on the table, 2 others died on the day of operation, 2 died 2 days, and the others 2 and 6 weeks after operation. One patient entered the hospital in coma and died before surgery could be undertaken.

The clinical diagnoses made on admission were as follows:

Acoustic nerve tumor	8
Cerebellopontine angle tumor	2
von Recklinghausen's disease	1
Brain tumor	3
Undetermined	1

CRANIOPHARYNGIOMA (ADAMANTINOMA)

Eight of the 446 intracranial tumors were classified as craniopharyngiomas. All of them occurred in males; 5 were white, 2 Negroes and 1 unknown; the average age was 28.6 years.

All craniopharyngiomas were located in the region of the sella turcica. These tumors arise from the remnants of craniopharyngeal ducts; they are cystic and have varying amounts of calcium deposited in their walls. Their lumens are filled with yellow grumose material containing cholesterin crystals. These tumors are usually well encapsulated but may invade the surrounding brain substance, and at times extend into the 3rd ventricle (Fig. 86-88).

Histologically, craniopharyngiomas fall into 3 groups: (1) Squamous papillary epithelial cysts which are characterized by numerous papillary projections lined by squamous epithelium; (2) Adamantinomas which are characterized by epithelial cells arranged in columns, resembling the pattern of the embryonic enamel organ. The basilar layer of columnar cells (ameloblasts) later becomes stratified. Stellate cells are prominent in the connective tissue cores of the epithelial columns (Fig. 90 and 91); (3) Rathke's pouch cysts which are characterized by a thin fibrous wall containing flecks of calcium. The lining is composed of ciliated columnar and goblet cells.

Squamous papillary cysts are suprasellar and compress overlying structures. Adamantinomas tend to invade the sella turcica and destroy the hypophysis. All the tumors arise in the region of the sella turcica and extend into the chiasm, temporal lobe, and sphenoid bone. The interval from onset to the diagnosis is as follows:

Time	Number	Per Cent
Less than 1 week	1	12.5
1-8 months	3	37.5
8-12 months	3	37.5
Over 1 year	1	12.5
	8	100.0

The most prominent presenting symptoms were related to intracranial pressure and included headache, lethargy, nausea, vomiting, and coma. In addition, there were visual symptoms, such as bitemporal blindness and progressive loss of vision; and symptoms of dwarfism and obesity related to pituitary dysfunction.

The preoperative roentgenograms showed enlargement of the sella turcica in 3 cases and erosion in 1.

Craniotomy was performed in 6 cases. Death occurred on the first day after operation in 1 case, the fourth day in another. One patient died of pulmonary embolus from thrombophlebitis on the seventh day.

The clinical diagnoses were:

Tumor of chiasm	3
Suprasellar brain tumor	2
Pituitary tumor	2

HEMANGIOBLASTOMA (HEMANGIOENDOTHELIOMA)

Seventeen of the 446 intracranial lesions were classified as hemangioblastomas, making up 3.8 per cent. Fourteen were found in males and 3 in females. All the patients were white, and the average age was 30.7 years.

Hemangioblastomas occur most frequently in the cerebellum. They commonly are cystic, and often have a mural nodule, which nearly always is located on the pial side of the cyst. Some are solid or contain only a few small cystic areas (Fig. 89). The surrounding brain is usually compressed but may be invaded. The microscopic picture is charac-

terized by masses of immature vessels, and proliferation of dilated endothelial lined spaces. The spindle-shaped endothelial cells composing the lining often fuse to form giant cells. The capillary endothelium proliferates to form irregular cellular buds. A few of the cells may show the intracytoplasmic fenestrations or channels (Fig. 92-94). Mitotic figures are fairly common. The Perdrau stains brings out a prominent reticulum network. Foam cells are scattered between the vascular spaces. The tumors may be classified as capillary, cavernous, or cellular hemangioblastomas.

Hemangioblastoma of the cerebellum may be associated with angiomas of retina and cysts of the pancreas and the kidneys and represent the condition known as von Hippel's or Lindau's disease. On occasion, hypernephroma and angioma of the liver and spinal cord are also seen in these diseases. Another condition related to hemangioblastoma is Sturge-Weber's disease characterized by facial nevus, glaucoma, and epilepsy.

The hemangioblastomas were located as follows:

	Right	Midline	Left	Unspecified
Cerebellum	6	1	6	1
Frontal lobe	1		1	
Temporal lobe	1		0	

The tumors of the left frontal lobe extended into the parietal and temporal lobes and that of the right frontal into the lateral ventricle.

The duration from onset of symptoms to the diagnosis varied from 1 week to 13 years.

	Number	Per Cent
1-4 weeks	5	29.4
1-2 months	2	11.7
3-5 months	4	23.7
6 months-1 year	3	17.6
Over 1 year	1	5.9
Unknown	2	11.7
	17	100.0

History of trauma incurred 3 and 7 years before onset of symptoms was present in 2 cases.

The presenting symptoms and signs were usually related to the cerebellum, with headache predominating. Vomiting, ataxia, vertigo, nausea, papilledema, stiff neck, nystagmus,

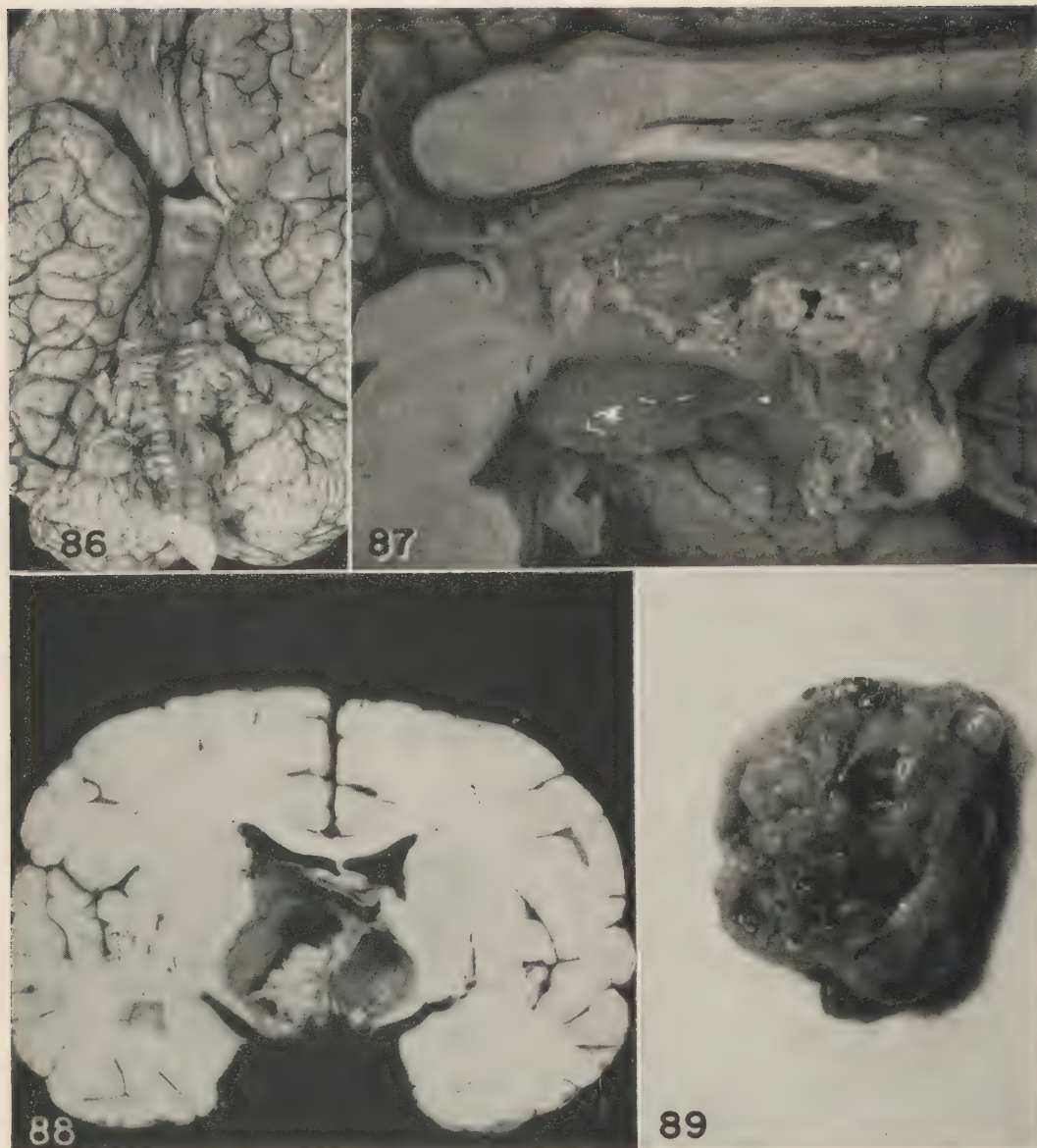


FIG. 86. A craniopharyngioma lying just posterior to the optic chiasm and projecting into the 3rd ventricle. Note the gelatinous appearance of the tumor. AIP Neg. 89296.

FIG. 87. A cross section of same tumor showing gelatinous material and distinct excrescences of tumor projecting into the cystic cavity. AIP Neg. 89296.

FIG. 88. Craniopharyngioma: a solid tumor mass projecting into the cystic space formed by the tumor. AIP Neg. 77735.

FIG. 89. A surgical specimen of a mural nodule of a hemangioblastoma of the cerebellum. AIP Neg. Br 94-43.

blurring vision, slurring speech, psychosis, and coma were reported in many of the cases.

Retinal lesions were described in 1 case and specified as absent in 1 other; no mention was made of the retina in 15 cases. Two cases were

diagnosed as Lindau's disease and cysts were described in kidneys and pancreas. One case was called von Hippel's disease without qualifying statements.

Craniotomy was performed in 14 cases.

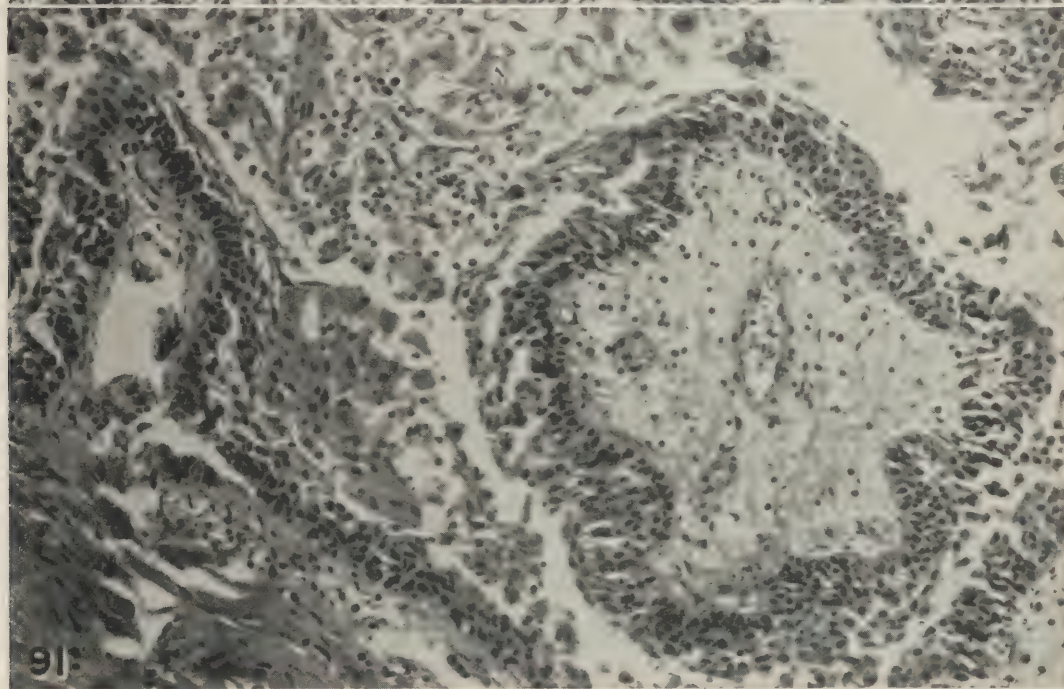
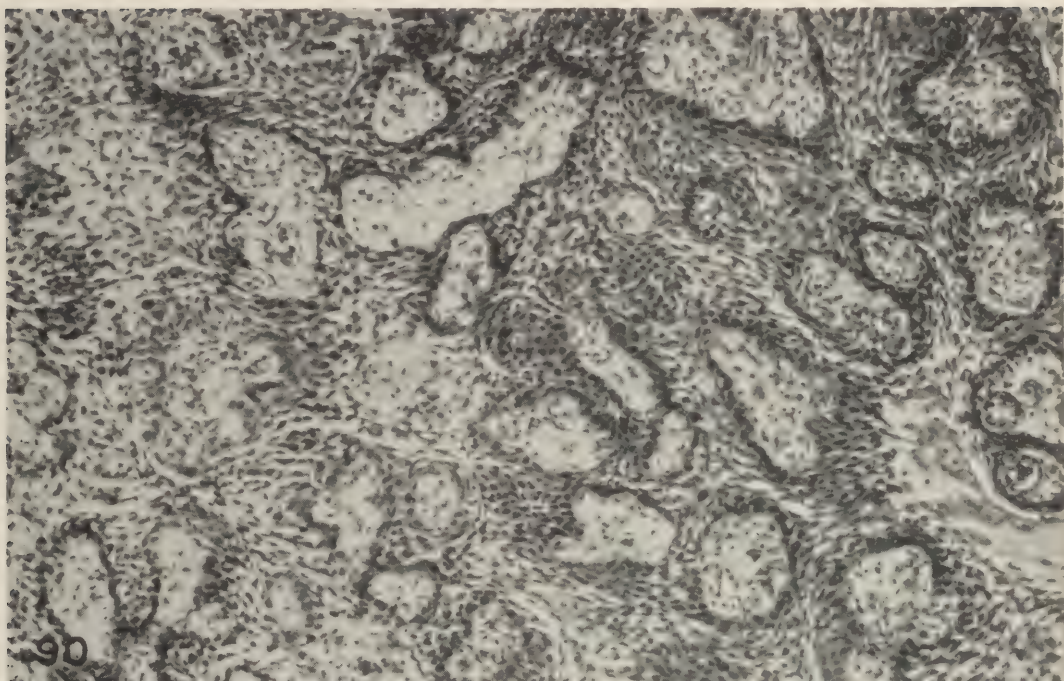


FIG. 90. Craniopharyngioma (adamantinoma). $\times 160$. AIP Neg. 96349.

Fig. 91. Craniopharyngioma: the characteristic squamous cells are derived from the multilayered basal cells. $\times 160$. AIP Neg. 96315.

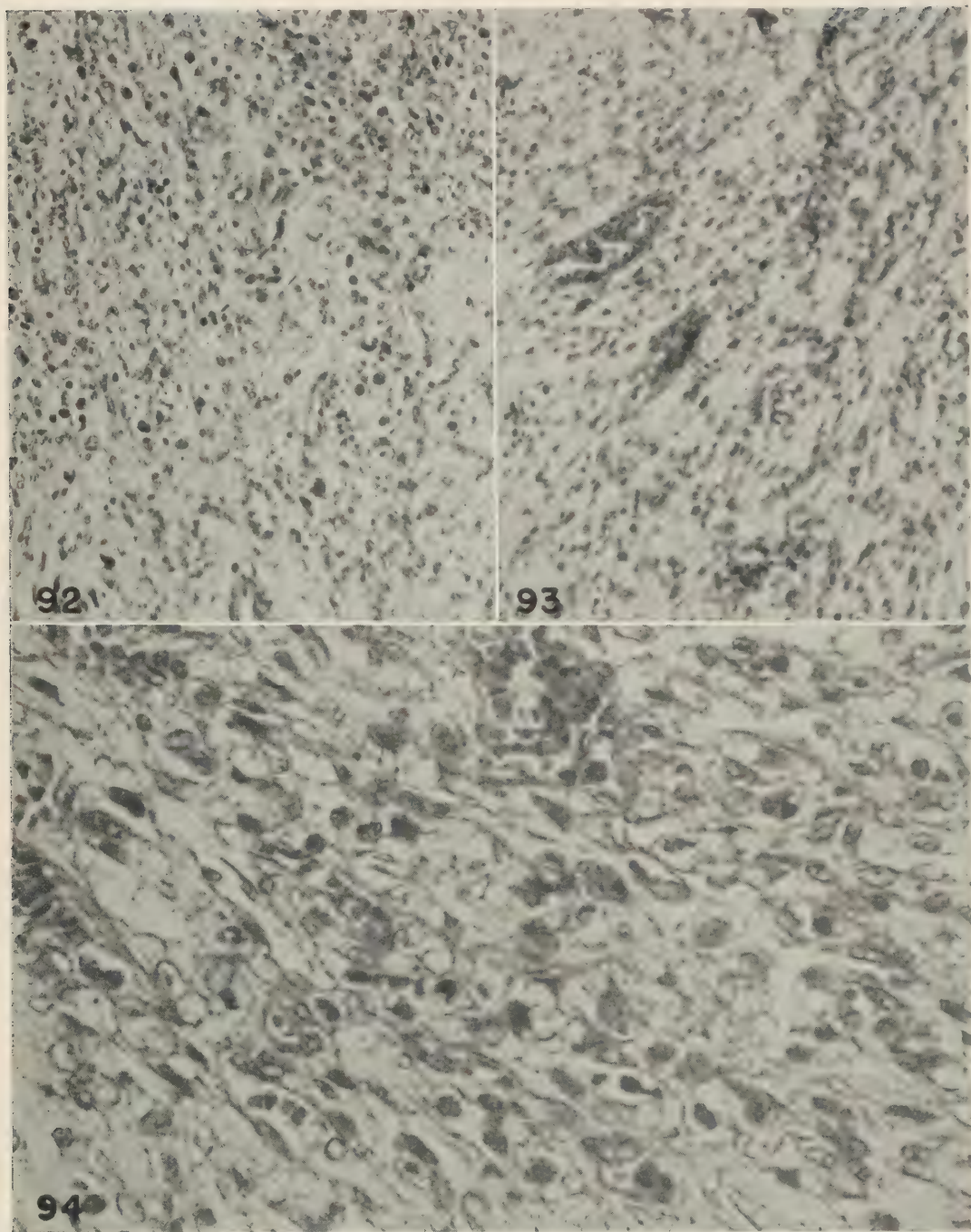


FIG. 92. Hemangioblastoma of cerebellum; the immature vascular channels are separated by numerous spindle-shaped cells and a fine reticulum. $\times 210$. AIP Neg. 96177.

FIG. 93. Hemangioblastoma of cerebellum: the cells of tumor appear to be part of formation of vascular channels. An occasional mitotic figure is seen. $\times 210$. AIP Neg. 96176.

FIG. 94. Hemangioblastoma of cerebellum: a higher magnification showing the vascular channels and intracytoplasmic channels. $\times 550$. AIP Neg. 96155.

Two patients died before operation could be performed, one of meningitis, the other of sagittal sinus thrombosis secondary to otitis media. There were 4 postoperative deaths; 2 on the day of operation, one 2 days later, and another after 23 days.

The clinical diagnoses included:

Brain tumor	6
Cerebellar tumor	8
Hypertensive encephalopathy	1
Recurrent hemangioendothelioma (cerebellum)	1
Meningoencephalitis	1

SARCOMA

Five, or 1.1 per cent, of the intracranial neoplasms were classified as sarcomas. All the tumors were in white males, 23, 25, 31, 32 and 33 years of age, making an average of 28.8 years.

Malignant meningiomas (meningiomas) have been included with meningiomas and malignant neurofibromas (neurofibrosarcomas) with neurofibromas.

The solid tumor may be diffuse and spread over the surface of the brain or form a more compact mass which invades the surrounding tissues (Fig. 29).

This group of tumors includes lesions variously called sarcoma, angiosarcoma, gliosarcoma, endotheliomatosis, perithelioma, periendothelioma, and perivascular sarcoma. Abbott and Kernohan¹ described 3 types of primary sarcomas of the brain, namely: (1) fibrosarcomas, (2) perivascular sarcomas (perithelial or adventitial sarcomas), and (3) sarcomas of unknown type.

Fibrosarcoma is characterized by spindle or plump oval cells lying in a matrix of collagen and reticular fibrils. At times, pseudo-alveolar arrangement about small blood vessels is accompanied by myxomatous degeneration.

Perivascular cellular tumor consists of small round and oval cells with abundant eosinophilic cytoplasm and hyperchromatic atypical nuclei. The vessels, which are increased in number, are surrounded by a fine reticulum. The cells form perivascular rings or collars (Fig. 97-99).

Sarcoma of undetermined origin presents a variable picture and does not fall into the other specific categories (Fig. 96).

The sarcomas in our series were classified as fibrosarcoma (3), perivascular sarcoma (1), and primary melanosisarcoma (1).

A clinical diagnosis of brain tumor was made in all 5 cases.

The primary location of sarcomas was difficult to ascertain for a majority were rapidly growing and very invasive. Three were predominantly in the right frontal area and one of these had extended into the meninges and the lateral ventricle. Another had extended across the midline by way of the corpus callosum and invaded the opposite frontal lobe. A tumor of the 3rd ventricle had invaded the brain stem.

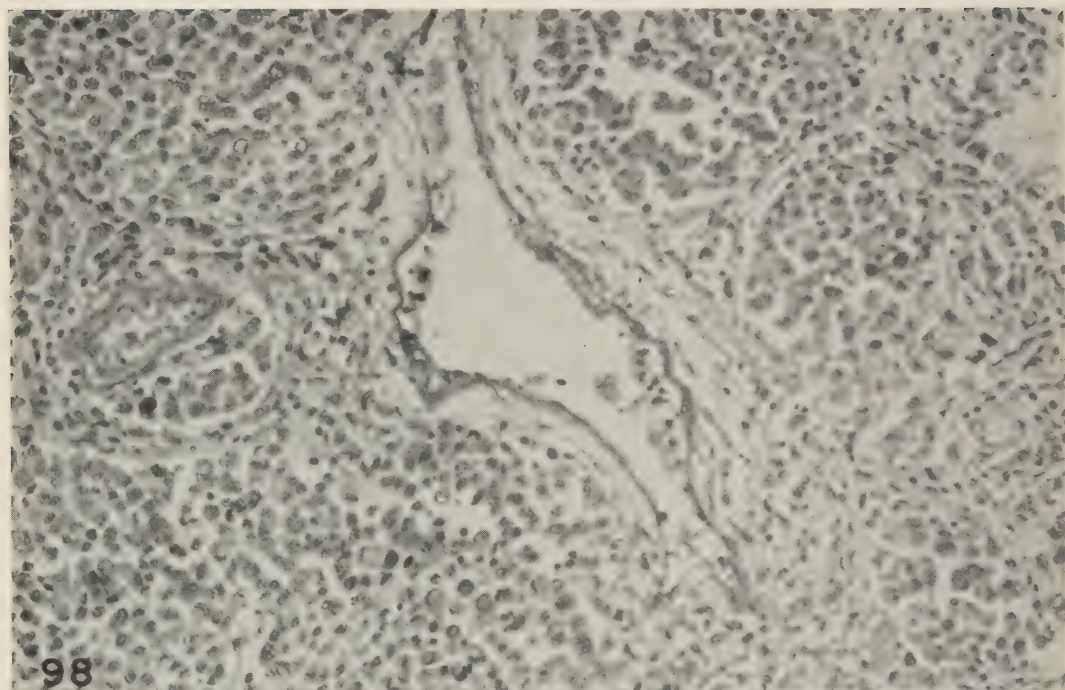
The interval from onset to diagnosis was short, varying from 5 weeks to 4 months; in 4 of the 5 cases, it was less than 3 months.

The presenting symptoms and signs were as complex as in the other brain tumors, with headache and papilledema in every case and nystagmus in 2. Dizziness, nausea, vomiting, lethargy, coma, stupor, loss of vision, hemiopia, and Jacksonian convulsions were additional symptoms.

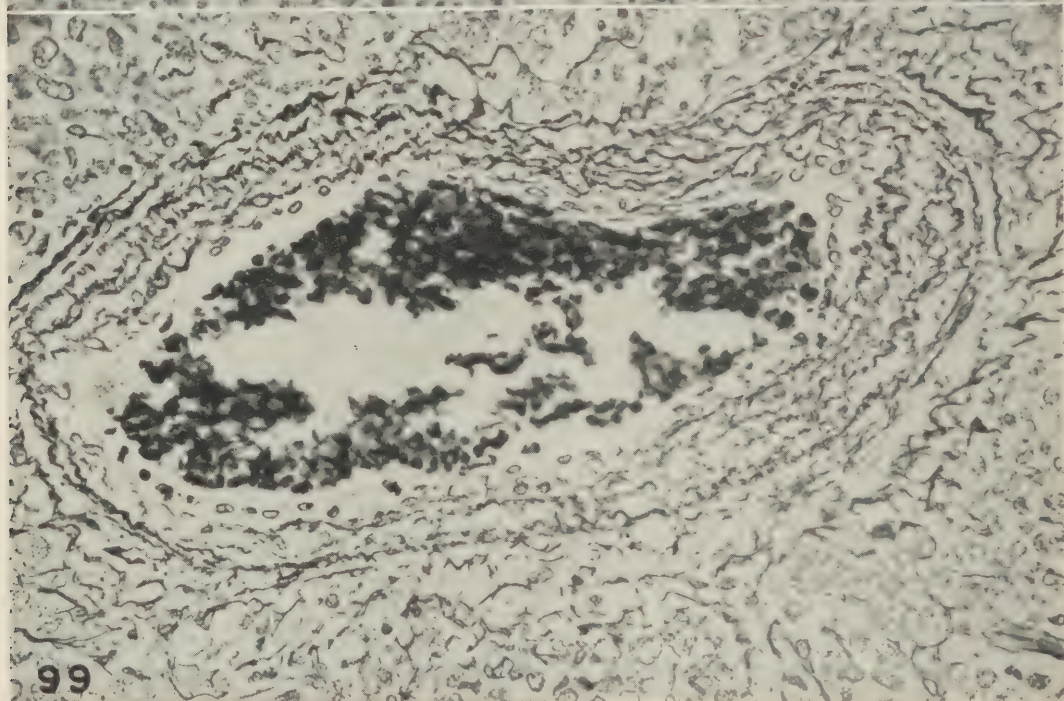
Craniotomy was performed in 4 cases and ventriculogram in 5. One patient died after ventriculography and before craniotomy could be performed, because of hemorrhage into the tumor. Two patients died, 1 day after operation from shock and surgical trauma, another 7 days postoperatively from pneumonia.

CYSTS

There were 16 cystic tumors in all, or 3.6 per cent of the series. "Colloid" cysts of 3rd ventricle (paraphysal cysts), make up the bulk of this group, but cerebral cysts of undetermined origin and a pituitary stalk cyst are also represented. All incidental cysts of the choroid plexus were omitted from this study. Twelve colloid cysts of the 3rd ventricle comprise 2.7 per cent of the series under consideration. Three (0.7 per cent) cysts were found in the cerebral cortex and one in the pituitary stalk.



98



99

FIG. 98. Sarcoma: the cells about the vessels have abundant cytoplasm with eccentric nucleus. These cells are intimately related to the vessels. $\times 230$. AIP Neg. 96151.

FIG. 99. The Perdrau stain shows strands of reticulum intimately associated with the cells about the vessels. AIP Neg. 96187.

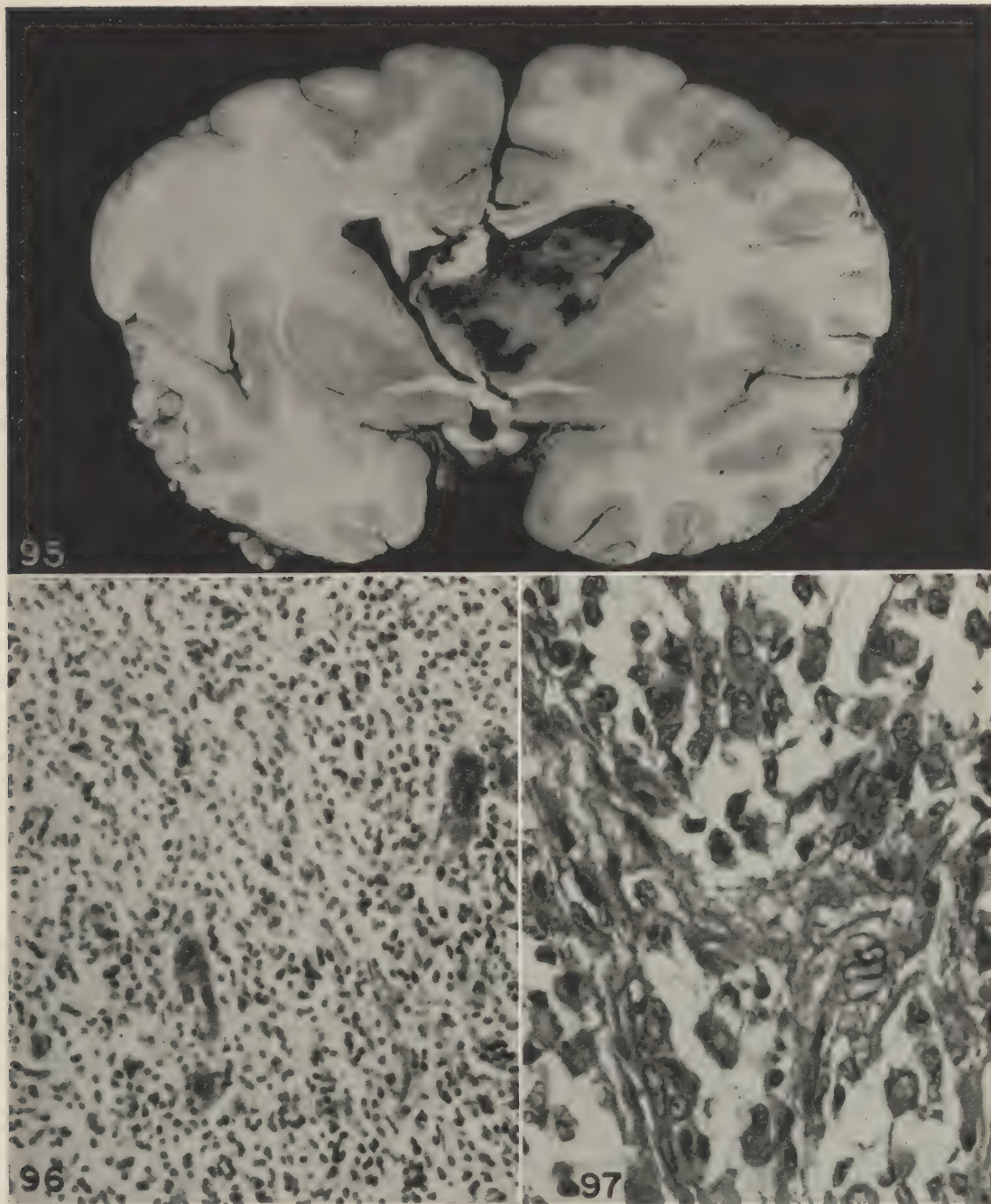


FIG. 95. Sarcoma: a soft hemorrhagic tumor indistinguishable from glioblastoma multiforme. AIP Neg. 90288.

FIG. 96. Sarcoma: the small atypical cells arranged around vessels appear similar to neuroblasts. No rosettes are seen. $\times 250$. AIP Neg. 96154.

FIG. 97. Sarcoma: the elongated cells with abundant cytoplasm are closely adherent to the blood vessels. This represents a perivascular sarcoma, $\times 700$. AIP Neg. 93125.

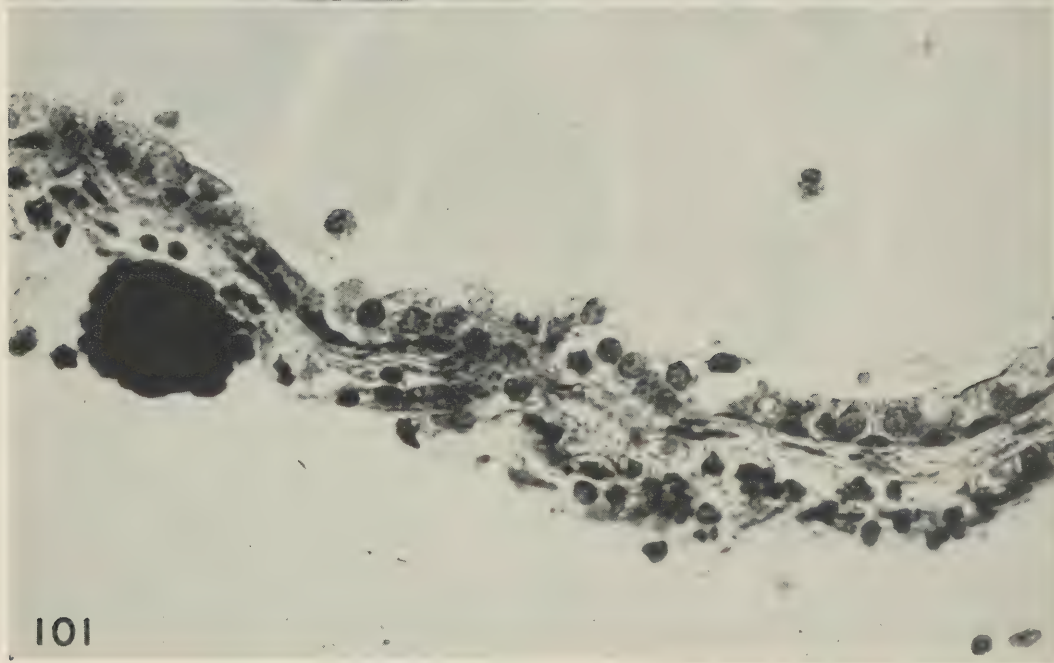
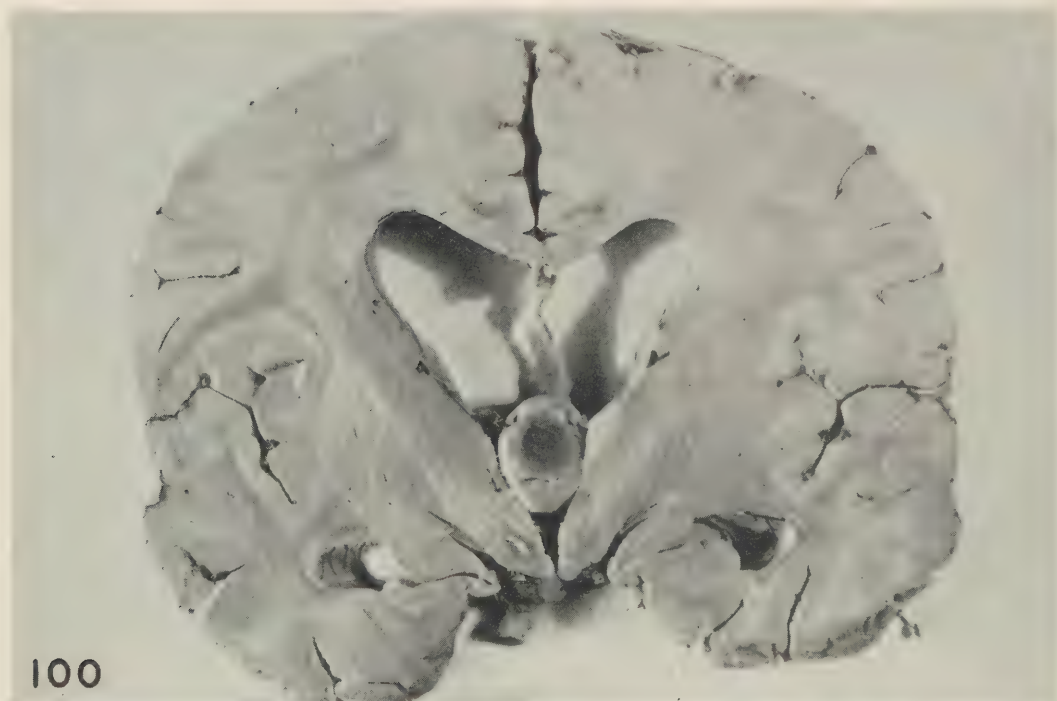


FIG. 100. Paraphysal (colloid) cyst of 3rd ventricle. AIP Neg. 89784.

FIG. 101. "Colloid Cyst": The wall of cyst is lined by cuboidal epithelium resembling the cells of choroid plexus. Note the psammoma body in the wall. AIP Neg. 96281.

Colloid cysts: (Paraphysial cysts, 3rd ventricle cysts). Colloid cysts were present only in men, 11 white and 1 Negro, with an average age of 23.8 years. In this series 9 were in the 3rd ventricle and 3 in the septum pellucidum; 3 cysts were multiple.

The cysts are smooth, round, and attached to the wall of the ventricle by a delicate fibrous stalk or pedicle; their walls are thin; they are filled with a homogeneous "colloid" material (Fig. 100). The internal lining is smooth and glistening. The thin connective tissue wall is lined by a layer of cuboidal epithelial cells, and is often hyalinized. The nuclei of the cells are large and vesicular (Fig. 101).

The colloid cysts probably develop from the primordium of the paraphysis and according to Moss¹⁶ and others should be called paraphysial cysts.

The duration from onset to diagnosis was as follows:

<i>Time</i>	<i>Number</i>	<i>Per Cent</i>
Less than 1 week	5	41.7
2-4 weeks	3	25.0
Over 1 month	3	25.0
Not given	1	8.3
	—	—
	12	100.0

The most frequent symptom present at the time of initial examination was periodic headache in 7 cases, followed by nausea, vomiting and papilledema in 5 each, convulsions in 3, dizziness, blurring of vision, and stupor in 2 each, and sudden unconsciousness, diplopia, marked rigidity and blindness in 1 case each.

Craniotomy was performed in 4 cases; 1 patient died 1 day after operation. Sudden death in the absence of surgical procedures occurred in 7 cases, coming 1 to 48 hours after sudden onset of symptoms. An hour after he had run in a foot race one patient suddenly collapsed and died.

The clinical diagnoses made were brain tumor in 4, hydrocephalus, meningitis, tumor of 3rd ventricle, septicemia, malaria, and in 3 cases no diagnosis was offered.

Cerebral Cysts: Three cerebral cysts were studied. All were in men, 2 white and 1

Negro; these patients were 22, 23 and 24 years of age.

Sudden death occurred in one; in others onset was sudden and characterized by severe headache with progressive coma and death.

At the time of examination one patient complained of headache, nausea, vomiting, and dimming of vision which had been present for 3 months. The preoperative roentgenogram revealed a calcified mass in the left temporal region, which was removed at craniotomy.

The cysts were located in the left temporal and right occipital regions. In the cyst walls, marked gliosis with some fibrosis could be seen, but morphologic examination gave no clue as to origin of the cerebral cysts, although it is probable that they are porencephalic.

The pituitary stalk cyst was found in a patient who had had severe headaches for about 10 years, and continuous pain in the neck for the last 4 years. Just before admission a bilateral hemianopsia was discovered. At craniotomy a 5 mm. cyst was found in the stalk of the pituitary, and hydrocephalus was noted. After removal of the cyst, which was lined with flattened cuboidal epithelium, the patient made an uneventful recovery.

HEMANGIOMA

Only those tumors are included in this series which had given rise to symptoms or were directly responsible for death. Thirty hemangiomas fulfilled these requirements. This represents 6.7 per cent of the 446 intracranial tumors studied. Twenty-nine occurred in males, 1 in a female; 26 patients were white and 4 Negro; their average age was 30.0 years.

The differentiation of hemangiomas and telangiectasis is difficult. The hemangiomas include true arterial or venous angiomas. Although these tumors may be considered congenital anomalies, they are here classified as tumors.

Hemangiomas are divided into capillary or cavernous, arterial or venous, depending on the type of vessel which predominates. These tumors may be isolated or diffuse. They are

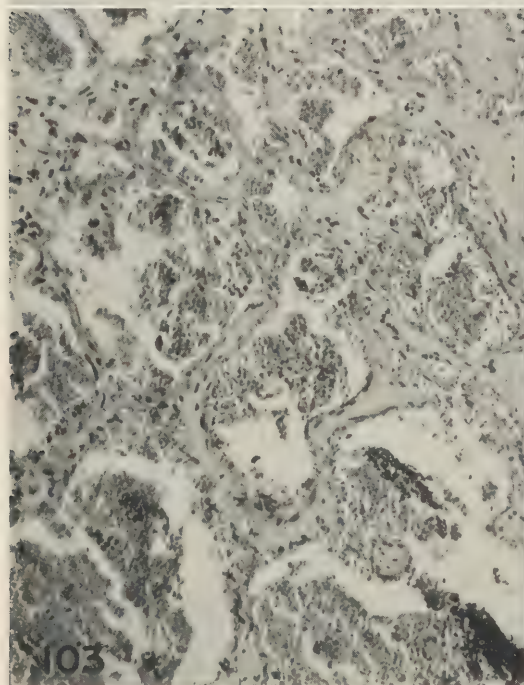


FIG. 102. Hemangioma: The vascular lesion is located in the right temporal region. Note the dilated vessels in the meninges and the close approximation to the ventricle. AIP Neg. 82345.

FIG. 103. Hemangioma: The vascular spaces are separated by dense hyalinized connective tissue. Note the variations in size of channels. $\times 50$. AIP Neg. 92839.

FIG. 104. Hemangioma: The vascular channels are both arterial and venous. Note the intimal proliferation in some channels. A recent thrombosis is also seen. $\times 60$. AIP Neg. 96282.

usually composed of both arterial and venous channels and form wedge-shaped, blood-filled masses with the apex pointing toward the center of the brain and the base lying along the pia arachnoid. On cross section the dilated blood channels are seen to be separated by varying amounts of connective tissue. Small masses of irregularly coiled vessels may extend into, or compress, the surrounding structures (Fig. 102). Many of the tumors contain thrombi and old blood pigment in macrophages. Hemorrhage is frequently seen in the brain tissue about the angiomas. The intimal surfaces may show proliferation with fragmentation and duplication of the internal elastic lamina. The media is usually distorted and in some channels is completely absent (Fig. 103-104). Calcification is often present in any or all of the layers. A marked glial reaction often surrounds this tumor, leading to mistaken diagnosis of vascular glioma; the gliosis, however, is a response to a vascular tumor rather than to a primary neoplastic process.

The lesions were classified as follows:

Hemangioma	21
Venous angioma	2
Cavernous angioma	4
Calcified angioma	1
Racemose angioma	1
Cystic hemangioma	1
	—
	30

Hemangiomas were located as follows:

	<i>Right</i>	<i>Midline</i>	<i>Left</i>
Cerebellum	6	1	5
Frontal lobe	3		3
Parietal lobe	6		2
Temporal lobe	0		2
Occipital lobe	3		1
Basal nucleus			1
Pons	1		
Choroid plexus	1		

Four hemangiomas approximated the border of the ventricular systems. Two tumors from the periphery of the brain had extended into the basal nucleus, one had involved the scalp and bone, and a cerebellar lesion had extended into the midbrain.

Duration from onset of symptoms to diagnosis was as follows:

	<i>Number</i>	<i>Per Cent</i>
Less than 1 week	14	46.7
1-4 weeks	2	6.7
1-2 months	3	10.0
3-6 months	6	20.0
6 months-1 year	3	10.0
Over 1 year	1	3.3
Unknown	1	3.3
	—	—
	30	100.0

In the majority of the cases onset was sudden with headache or a brief period of unconsciousness immediately before death. Significant trauma preceded death by a week or two in 2 cases; exercise was related to the onset of symptoms in 3. Two deaths occurred during sleep and one during heat treatment for gonorrhea. Sudden unconsciousness in 16 cases was preceded most often by headache but also by convulsions, exercise, sleep, vomiting, vertigo and hemiplegia. Other symptoms and signs related to increased intracranial pressure were recorded in many of the cases.

Sudden death occurred in 24, and in 21 was caused by hemorrhage which was cerebral, intraventricular, subarachnoid, or subdural. The cause of death in 3 cases was not determined. Craniotomy was performed in 10 cases with one postoperative death on the seventh day.

Intracranial hemorrhage and intracranial tumor were the diagnoses in the majority of cases; others were tumor with hemorrhage, acute poisoning, cardiac failure, and schizophrenia. Calcification of the tumor was demonstrated by roentgen examination in 3.

PAPILLOMA OF THE CHOROID PLEXUS

Three papillomas of the choroid plexus were found, representing 0.7 per cent of the series. These tumors occurred in white males, one 19, one 22, and a third 27 years of age.

Papillomas of the choroid have been included among the ependymal tumors by Globus and Kuhlenbeck⁸; however, they arise from the choroid plexus and are morphologically distinct tumors.

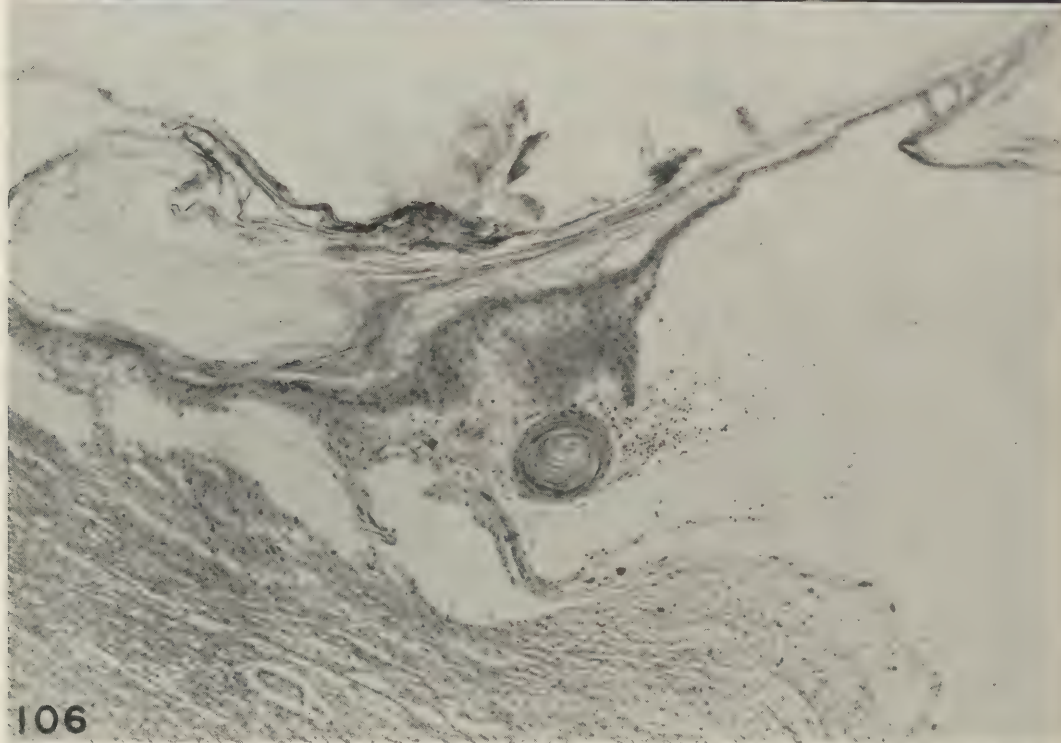
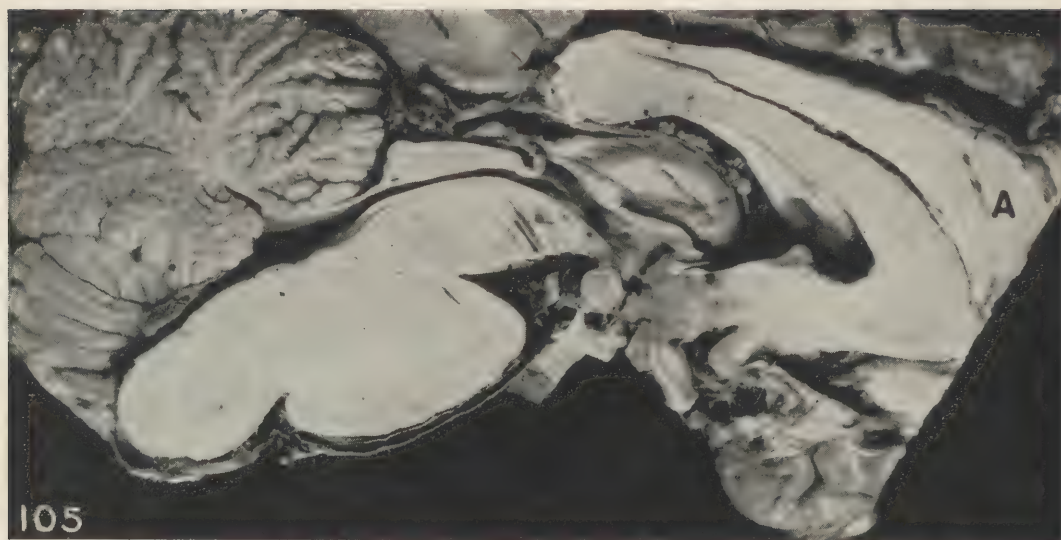


FIG. 105. The lipoma (A) lies immediately above the corpus callosum and assumes a triangular flat shape. AIP Neg. 85152.

FIG. 106. Epidermoid: Its wall consists of stratified squamous epithelium lying on a thin vascular connective tissue base. The cysts contain kerato-hyaline material. Note the "daughter" cyst. AIP Neg. 72061.

The tumors grossly are typical papillomas with vascular connective tissue cores; they are often cystic. The epithelium, which resembles that on the surface of the villi of the choroid plexus, arises directly from the medullary

epithelium. It is not ciliated and does not contain the so-called "blepharoplasts"* seen in

* The structures called blepharoplasts by various authors correspond to the basal corpuscle of ciliated epithelium including ependyma.

the ependymal epithelium. The cells are cuboidal and have large oval nuclei and coarsely granular cytoplasm; they are placed evenly about a central vascular core of con-

One patient died 2 months after operation. No follow-ups are available on the other 2 cases.

A diagnosis of brain tumor was made in 2 cases.

TABLE I

CLASSIFICATION		SOURCE OF INFORMATION												
		Cushing 1932			Baker 1943			A.I.F. 1946			Fividge, Penfield & Stone 1953		Sailly 1953	
		No. Cases	% Tumors	% Gliomas	No. Cases	% Tumors	% Gliomas	No. Cases	% Tumors	% Gliomas	No. Cases	% Gliomas	No. Cases	% Gliomas
I. Gliomas		462	46.3		351	61.8		281	62.3		210	(44.9)	445	
	A. Unclassified	175	9.3		6	1.0		3	0.7		20	9.5	69	17.8
	B. Classified	687	36.6		375						190		376	
	1. Glioblastoma multiforme	208	11.2	30.3	102	16.4	27.2	102	22.9	36.6	52	27.4	117	30.9
	2. Astrocytoma	255	13.6	37.1	156	26.9	44.3	63	14.1	22.5	56	29.5	156	38.9
	3. Medulloblastoma	86	4.6	12.5	25	4.1	6.7	45	10.2	16.2	28	14.7	55	14.6
	4. Astroblastoma	35	1.9	5.1	16	2.6	4.5	6	1.3	2.2	13	6.8	20	5.3
	5. Spongioblastoma polare	32	1.7	4.7	11	1.8	2.9	13	2.9	4.7	11	5.8	12	3.2
	6. Oligodendroglioma	27	1.4	3.9	12	1.9	3.2	14	3.2	5.0	8	4.2	12	3.2
	7. Ependymoma	25	1.3	3.6	32	5.2	8.5	14	3.2	5.0	19	10.0	16	4.2
	8. Pinealoma	14	0.7	2.0	7	1.1	1.9	13	2.9	4.7	2	1.1	8	2.1
	9. Gangliocytoma	3	0.2	0.5				6	1.3	2.2			1	0.3
	10. Neuroepithelioma	2	0.1	0.3	4	0.6	1.0	1	0.2	0.4	1	0.5	1	0.3
	11. Ependymoblastoma							1	0.2	0.4				
II. Pituitary Adenomas		360	19.2		29	4.5		29	5.8					
	1. Chromophobe	264	14.1					22	4.9					
	2. Chromophilic	3	0.2					3	0.7					
	3. Mixed	25	1.2					1	0.2					
III. Meningioma		271	14.6		122	17.8		34	6.7					
IV. Acoustic Nerve Tumors (Neuroma)		176	9.5		13	2.1		15	3.4					
V. Congenital Tumor		113	6.0		22	3.6		12	2.7					
	1. Craniopharyngioma	92	4.9		16	2.6		8	1.8					
	2. Cholesteatoma and Dermoid	15	0.8		5	0.8		4	0.9					
	3. Chondroma and Teratoma	6	0.3		1	0.2								
VI. Blood Vessel Tumors		41	2.2		37	6.0		47	10.5					
	1. Hemangiomas				23	3.7		30	6.7					
	2. Hemangioendotheliomas				14	2.3		17	3.8					
VII. Sarcomas		14	0.7					5	1.1					
VIII. Papilloma, Choroid Plexus		12	0.6					3	0.7					
IX. Miscellaneous														
	1. Unclassified Tumors, Brain	17	0.9		13	2.2		2	0.4					
	2. Cysts	6	0.3					16	3.6					
TOTALS		1,872	100.0		616	100.0		446	100.0					

nective tissue which often is myxomatous. The papillomas occasionally may be implanted along the ventricular system.

The duration of symptoms varied from 3 to 9 months. Headache and papilledema were present in all cases, nystagmus, dimming of vision, scotoma, and dizziness each occurred once.

Craniotomy was performed in every case. Two of the lesions were located in the 4th ventricle and the other in the 3rd ventricle.

LIPOMA

Of the 446 tumors 2 were lipomas. Both occurred in white men, one 18, the other 26 years of age. The tumors were incidental findings in both cases, one in a man killed by a stab wound in the heart, the other in a man who died from phosphorus burns after a bomb explosion.

The lipoma in one case was located in the meninges, the usual site; the other tumor was located on the superior surface of the corpus

callosum. Baker and Adams⁵ have reported lipomas in the tuber cinereum and midbrain.

The gross appearance of the elongated, encapsulated tumor is that of glistening yellow fat (Fig. 105).

Lipomas are made up of numerous mature fat cells with small areas of embryonic fat and a few macrophages containing lipid material.

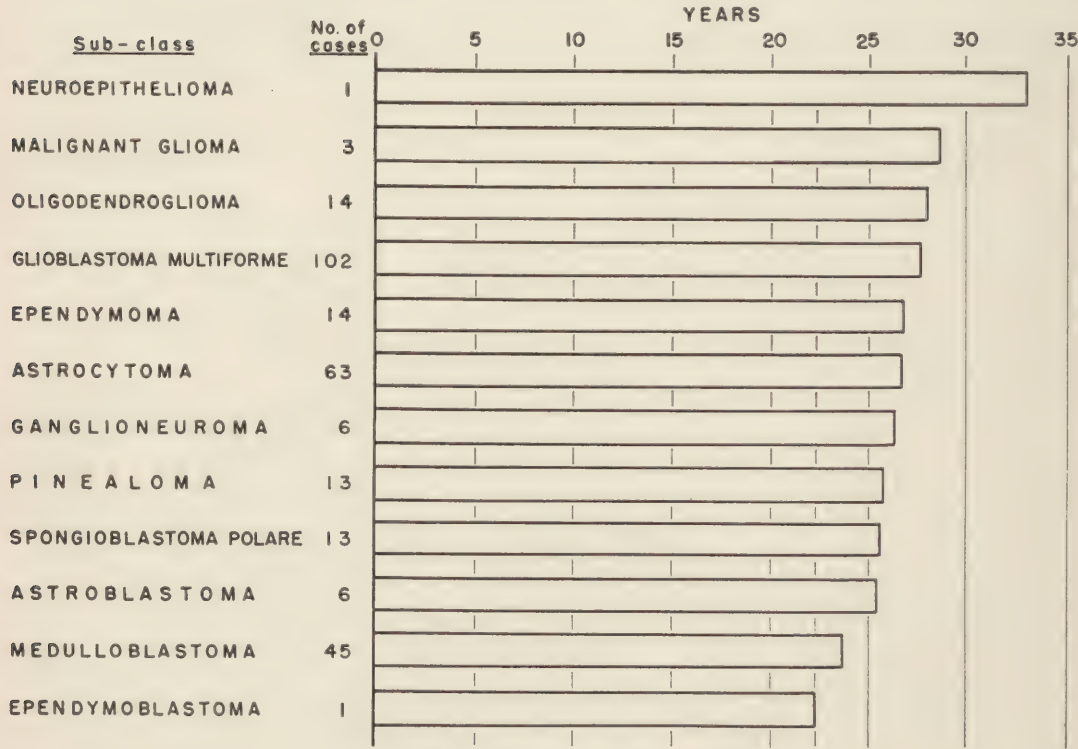
EPIDERMOID (CHOLESTEATOMA)

Four tumors classified as epidermoids were found in the entire series (0.9 per cent). These tumors occurred in white males, 19, 33, 37 and 38 years of age, with an average of 25.4 years.

The epidermoid tumor is circumscribed, nodular, and cystic, with a smooth external

TABLE 2

AVERAGE AGE OF PATIENTS WITH PRIMARY GLIOMAS, IN MILITARY AGE GROUP BY SUB-CLASSES, WORLD WAR II



Tumors of this variety on occasion resemble xanthomas. The theories of origin of lipomas set forth in the literature are: (1) that the component cells arise from lipid cells already in the pia mater; (2) that they are the result of fatty transformation of connective tissue; (3) that they arise by differentiation of pial cells toward embryonic fat (metaplasia), and (4) that they arise from embryonal remnants of fat.

surface resembling mother of pearl. The wall is made up of dense connective tissue lined by stratified squamous epithelium with characteristic intercellular bridges and kerato-hyaline granules. Its thin fibrous capsule may be calcified. The cavity of the cyst is filled with grayish white, soft, caseous material, composed of desquamated epithelial cells and debris containing cholesterol crystals. Epidermoids may be located anywhere in the cerebrum, but are

usually found at the base of the brain (Fig. 106).

Epidermoid tumors of the choroid plexus apparently arise from metaplasia of the choroid epithelium, while other epidermoids may arise from embryonic epithelial rests.

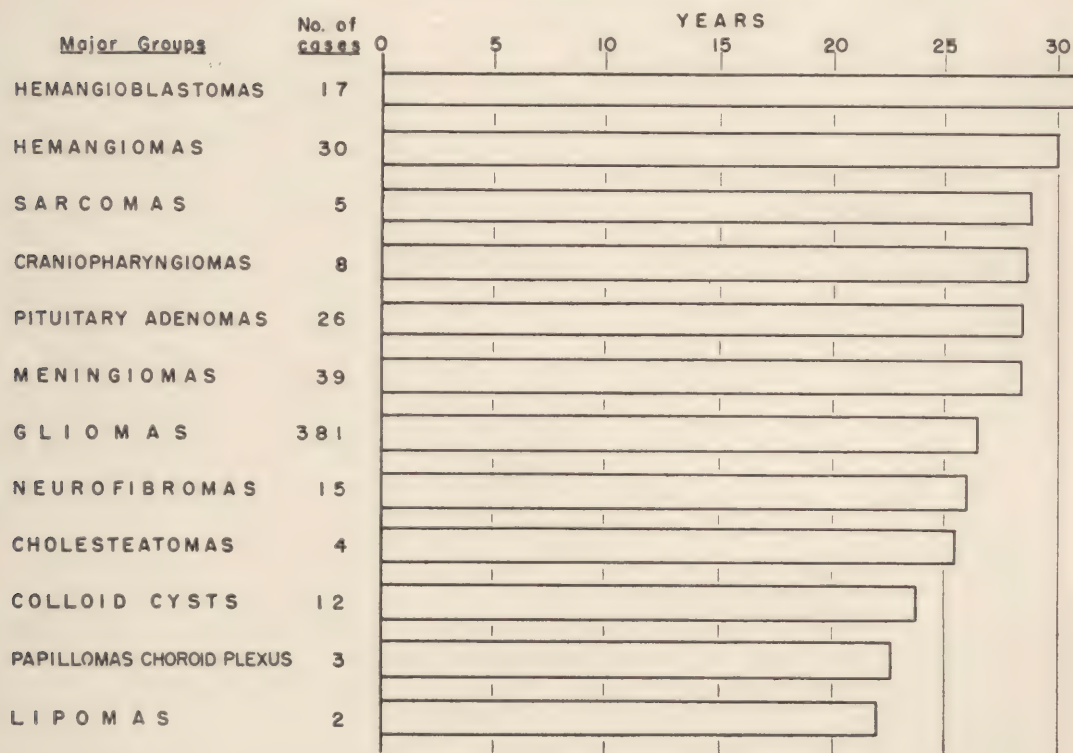
The tumors were located in the posterior fossa, inferior portion of the occipital lobe, and

age group, 18 to 38 years inclusive. The study is based on clinical records and material studied during World War II at the Army Institute of Pathology. An enumeration of the different types of tumors encountered is given in Table 1, in which comparison is made with other series.

The gliomas represented 62.9 per cent of

TABLE 3

AVERAGE AGE OF PATIENTS WITH PRIMARY INTRA-CRANIAL NEOPLASMS,
IN MILITARY AGE GROUP, WORLD WAR II



the choroid plexus. A tumor of the choroid plexus was related to symptoms in 1 case and was the cause of death in the other. The interval between onset of symptoms and diagnosis varied from 9 weeks to a year and a half. The symptom-complex included headache, blurring vision, papilledema, coma, and deafness associated with vertigo and tinnitus.

SUMMARY AND CONCLUSIONS

This survey is a summary of data on 446 intracranial tumors occurring in soldiers of the

the present series, with glioblastoma multiforme (22.9 per cent) the most frequent variety and astrocytoma (14.1 per cent) a close second. This ratio is reversed in other series based on different age groups. Medulloblastomas and pinealomas were more frequent and occurred in somewhat older persons in this series than in others. Ganglioneuromas were slightly more numerous, and the remaining gliomas were present in about the same ratio as recorded elsewhere.

In comparing the average age at which

TABLE 4
COMPARISON OF AVERAGE AGES OF PATIENTS
WITH GLIOMA

	Elvidge, Penfield & Cone ⁹	Army Institute of Pathology
Astrocytoma	29.5	26.5
Glioblastoma multiforme	41.2	27.6
Medulloblastoma	19.0	23.5
Ependymoma	29.0	26.6
Astroblastoma	32.0	25.1
Spongioblastoma polare	11.5	25.3
Oligodendroglioma	37.5	27.9
Neuroepithelioma	32.0	33.0
Pinealoma	12.0	25.4

tumors occurred in this series, with that in other statistical reports, one must remember that a selected age group is represented in this

TABLE 5
RACE OF PATIENTS WITH PRIMARY INTRACRANIAL
NEOPLASMS IN MILITARY AGE GROUP
WORLD WAR II

	White	Non-white*	Total
Intracranial neoplasms			
Glioma	253	28	281
Meningioma	36	2	38
Hemangioma	26	4	30
Pituitary adenoma	19	6	25
Hemangioblastoma	17	0	17
Cyst	14	2	16
Neurofibroma	15	0	15
Craniopharyngioma	5	2	7
Sarcoma	5	0	5
Cholesteatoma	4	0	4
Papilloma	3	0	3
Lipoma	2	0	2
Total Neoplasms	399	44	443
Gliomas			
Glioblastoma multiforme	93	9	102
Astrocytoma	59	4	63
Medulloblastoma	40	5	45
Oligodendroglioma	12	2	14
Ependymoma	13	1	14
Pinealoma	12	1	13
Spongioblastoma polare	9	4	13
Astroblastoma	5	1	6
Ganglioma	6	0	6
Malignant glioma	2	1	3
Ependymblastoma	1	0	1
Neuroepithelioma	1	0	1
Total Gliomas	253	28	281

*Note: Non-whites are all Negroes except for 4 Chinese and 1 Hawaiian.

series. The average ages are shown in Tables 2 and 3. It may be seen that the gliomas occur in earlier decades in this series than in those previously reported by Baker⁴ and Elvidge, Penfield and Cone.⁹

Neurofibromas (3.4 per cent) and meningiomas (8.7 per cent) were observed less fre-

TABLE 6
POSTOPERATIVE MORTALITY AMONG PATIENTS WITH
PRIMARY GLIOMAS IN MILITARY AGE GROUP
WORLD WAR II

Type of Glioma	Number of Patients Having Craniotomy	Number of Postoperative Deaths	Percent of Mortality
Pinealoma	11	7	63.6
Astrocytoma	54	29	53.7
Medulloblastoma	27	12	44.5
Glioblastoma multiforme	76	33	43.4
Oligodendroglioma	10	4	40.0
Ganglioneuroma	3	1	33.3
Spongioblastoma polare	7	2	28.6
Astroblastoma	4	1	25.0
Ependymoma	9	2	22.2
Ependymblastoma	1	0	0.0
Malignant Glioma	1	0	0.0
Neuroepithelioma	1	0	0.0
Total	204	91	44.6

quently than was expected. This relative variation is probably due to the fact that both of these tumors tend to develop more often in persons of more advanced age. Included in this survey were hemangiomas or vascular anomalies of hemangiomatous type, which gave rise to symptoms or caused death. Forty-seven such tumors (10.5 per cent of this series) were studied. Pituitary adenomas formed 5.8 per cent of the series, with the chromophobe variety greatly predominating. The other types of tumors in this series were relatively rare; they were: craniopharyngiomas (1.8 per cent); cholesteatomas (0.9 per cent); sarcomas (1.1 per cent); papillomas (0.7 per cent); lipomas (0.4 per cent), and cysts (3.6 per cent).

Race was specified in 443 cases. Three hundred ninety-nine of the tumors occurred in whites, and 44 in non-whites (39 Negro, 4 Chinese, 1 Hawaiian). The Negro population of the Army is approximately 10 per cent, which is comparable with the percentage of distribution of tumors occurring in this series.

TABLE 7

DURATION OF SYMPTOMS PRIOR TO ADMISSION
AMONG PATIENTS WITH PRIMARY INTRACRANIAL
NEOPLASMS IN MILITARY AGE GROUP
WORLD WAR II

(Percentage of patients with symptoms present 4 months and under prior to admission)

Types	Number of Patients with Known Duration of Symptoms	Number of Patients with Symptoms Present 4 Months and Less Prior to Admission	Per Cent
Glioma			
Ependyoblastoma	1	1	100.0
Glioblastoma			
multiforme	100	74	74.0
Medulloblastoma	42	29	69.0
Astroblastoma	6	4	66.7
Ganglioneuroma	4	2	50.0
Oligodendroglioma	13	6	46.2
Ependymoma	11	5	45.5
Astrocytoma	65	29	44.6
Pinealoma	11	4	36.4
Spongioblastoma			
polare	12	4	33.3
Total Gliomas	265	158	48.3
Sarcoma	5	5	100.0
Hemangioma	30	25	83.3
Hemangioblastoma	17	10	58.5
Meningioma	33	15	45.5
Pituitary adenoma	20	7	35.0
Craniopharyngioma	7	1	14.3
Neurofibroma	15	2	13.3
Total tumors other than gliomas	127	65	51.2

Eighteen, or 4.0 per cent, of tumors were in females. This number is so small that no conclusions can be drawn as to sex incidence of intracranial neoplasms.

The mortality rate was greater in gliomas

than in the other major groups. The immediate mortality was directly related to the surgical procedures. Size and location as well as type of tumor are the most significant factors in the fatal outcome. In over 50 per cent of pinealomas and astrocytomas death occurred less than 1 month after operation. The postoperative deaths are analyzed in Table 6.

Ten per cent of the total deaths occurred after spinal puncture, encephalogram or ventriculogram, and before other operation could be undertaken. In the presence of increased intracranial pressure such procedures should be carried out with extreme caution. Other explanations of sudden death occurring before operation are: hemorrhage into tumors, pressure cone of the medulla oblongata caused by changes in hydrodynamics of the ventricular fluid by the tumor, edema of the brain affecting vital structures.

Correlation between location of tumor and symptoms was not attempted, but a tabulation of initial symptoms was made in each group. A large percentage of patients presented symptoms of increased intracranial pressure. Specific localizing symptoms were directly related to the region or structures involved.

The duration of symptoms in each type of tumor varied, depending on the location of the lesion and the rapidity of growth. The shortest course was in the cases of glioblastoma multiforme and sarcoma. The duration with hemangioma was also brief; in most cases death was due to hemorrhage resulting from the rupture of the vessels making up the tumor. In reference to intracranial neoplasm in general, the immaturity of the lesion was influential as well as location in determining the development and duration of symptoms.

This review has brought to light many problems regarding intracranial tumors which suggest detailed studies to be carried out in the future.

REFERENCES

- ¹ Abbott, K. H., and Kernohan, J. W.: Primary sarcomas of brain. *Arch. Neurol. & Psychiat.*, 50:43-66, 1943.
- ² Bailey, P.: *Intracranial Tumors*. Springfield, Illinois, Charles C Thomas, 1933.

⁵ Bailey, P., and Bucy, P. C.: The origin and nature of meningeal tumors. *Am. J. Cancer*, 15:15-54, 1931.

⁴ Baker, A. B.: *An Outline of Neuropathology*. Ed. 3. St. Louis, John S. Swift Co., Inc., 1943.

⁶ Baker, A. B. & Adams, J. M.: Lipomatosis of the central nervous system. *Am. J. Cancer*, 34:214-219, 1938.

⁶ Courville, C. B.: Intracranial tumors, their pathology, symptomatology, diagnosis and prognosis. Fiske Fund Prize Essay. Providence, Snow and Farnham Co., Inc., 1931.

⁷ Cushing, H.: *Intracranial Tumors*. Springfield, Illinois, Charles C Thomas, 1932.

⁸ Cushing, H., and Eisenhardt, L.: *Meningiomas, Their Classification, Regional Behavior, Life History and Surgical End Results*. Springfield, Illinois, Charles C Thomas, 1938.

⁹ Elvidge, A., Penfield, W., and Cone, W.: The gliomas of the central nervous system. A study of two hundred and ten verified cases. *A. Research Nerv. & Ment. Dis., Proc.* 16:107-181, 1935.

¹⁰ Globus, J. H., and Kuhlenbeck, H.: The subependymal cell plate (matrix) and its relationship to

brain tumors of the ependymal type. *J. Neuropath. and Exper. Neurol.*, 3:1-35, 1944.

¹¹ Globus, J. H., and Kuhlenbeck, H.: Tumors of the stratolenticular and related regions. *Tr. Am. Neurol. A.*, 67:214-219, 1941. *Arch. Path.*, 34:674-734, 1942.

¹² Globus, J. H.: Pinealoma. *Arch. Path.*, 31:533-568, 1941.

¹³ Hassin, G. B.: *Histopathology of the Peripheral and Central Nervous Systems*. Ed. 2. New York, Paul B. Hoeber, Inc., 1940.

¹⁴ Horrax, G., and Bailey, P.: Tumors of the pineal body. *Arch. Neurol. & Psychiat.*, 13:423-470, 1925.

¹⁵ Kuhlenbeck, H., and Haymaker, W.: Neuroectodermal tumors containing neoplastic neuronal elements: ganglioneuroma, spongioneuroblastoma and glioneuroma. (With clinico-pathologic report of eleven cases and discussion of their origin and classification.) *MILITARY SURGEON*, 99:273-292, 1946.

¹⁶ Moss, L. D.: Paraphysial Cyst of the Third Ventricle. *Arch. Path.*, 39:184-186, 1945.

¹⁷ Weil, A.: *Textbook of Neuropathology*. Ed. 2. New York, Grune and Stratton, 1945.



COCCIDIOIDOMYCOSIS: A STUDY OF 95 CASES OF THE DISSEMINATED TYPE WITH SPECIAL REFERENCE TO THE PATHOGENESIS OF THE DISEASE

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(With thirty-seven illustrations)

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I

INTRODUCTION, MATERIALS, AND METHODS

PRECEDING the outbreak of hostilities in 1941 and early in the war it became apparent that the Army would be necessarily concerned with the problem of coccidioidomycosis, a rare but disabling and often fatal disease. The natural adaptability of the terrain and the weather conditions of the Southwest led to the selection of this area for the concentration of large numbers of troops both for flying and for desert warfare training. Southern California, Arizona, New Mexico, and the western portion of Texas, areas in which coccidioidomycosis had been previously established as an endemic disease, became the site of these activities.

Recognition of the problem that this disease might be expected to present to the armed forces resulted in the early establishment of a carefully organized coccidioidomycosis control program. This consisted of (1) careful surveys of the areas which were to be used for training purposes before the location of Army installations, (2) the setting up of a carefully controlled epidemiologic program within the various military establishments, and (3) the establishment of a rigidly planned program for the study of cases of coccidioidomycosis developing in the armed forces in the endemic areas.

One of the important features of the control program, the clinical and epidemiologic aspects of which have been dealt with in detail in a syllabus on coccidioidomycosis prepared by Russell V. Lee, Lt. Col., M.C., and Norman Nixon, Major, M.C., for the Army Air Forces Western Flying Training Command, was the careful and complete post-mortem study of all persons dying of coccidioidomycosis in the Army hospitals and the subsequent accumulation of all of the data and the materials relating thereto at the Army Institute of Pathology for the purposes of review and analysis.

This report deals with a group of 95 cases of disseminated coccidioidomycosis accumulated at the Army Institute of Pathology between June 9, 1941, and January 31, 1946. In-

cluded are those cases which had been received before the institution of the Army training program; interestingly enough, there were only two. One of these was contributed by a physician in San Antonio, Texas, and the other by one in Los Angeles, California.

The occurrence of the first fatal case of coccidioidomycosis at a military installation was at the Letterman General Hospital, San Francisco, February 1941, in a Civilian Conservation Corps worker. This case was filed with the Army Institute on June 9, 1941, and represents the beginning of an extraordinary accumulation of material, the sources of which are listed in Table I.

A mere acquaintance with coccidioidomycosis usually has been considered sufficient for physicians outside the endemic areas. That this no longer holds true is obvious from the fact that this disease has now occurred in approximately 6,000 members of the armed forces in clinically recognizable form and probably in a far greater number as subclinical infection. These patients have been scattered literally throughout the world, each constituting a potential means of transplantation of this infection, which formerly was restricted to very small areas in North America, South America, and perhaps South Europe. These facts demand that every physician, especially those of the American profession, be fully informed with regard to this fungus infection. Although the primary purpose of this report is to present a comprehensive survey of the pathologic anatomy of coccidioidomycosis occurring in the armed forces for the use of the Office of the Surgeon General of the Army and allied agencies, it is hoped that the study of this large accumulation of material may at the same time extend our knowledge of the general pathology of this little-known disease.

No opportunity comparable to that presented by this war-time accumulation of material has previously been offered. The original description of the disease by Rixford and Gilchrist, although comprehensive and thorough, dealt with only two cases. The one report which preceded theirs was made by Wernicke

in 1892, and it recorded a single observation. Ophüls' thorough study of the problem in 1905 was also based on a small number of cases and an even smaller number of autopsies. According to Bancroft, at this time only 89 cases of this disease were on record, 49 of them fatal. Thus in 1905 a large series of cases could not have been studied post mortem. In 1929 Evans and Ball reported 18 autopsies, the largest series on record. At the time of this study, 175 cases were known to have been seen clinically; but, according to Pulford and Larson, only 101 of these had been reported. In 1936 Abbott and Cutler were able to find only 36 post-mortem studies of coccidioidomycosis among 12,000 autopsies at the Los Angeles General Hospital. This yet unpublished group of cases probably represents the largest single accumulation of post-mortem material in existence previous to the outbreak of the war, since the Los Angeles General Hospital is within the area in which the disease was first discovered, and also in the area in which the largest number of clinical cases has occurred. (The Health Department of California in 1939 had on record a total of 660 cases of coccidioidomycosis, the vast majority of which had occurred in the San Joaquin Valley of south central California. This figure is particularly important as an indication of the incidence of the disease, which has been reportable in California since about 1930.) In 1942 Benninghoven and Miller stated that only 125 cases of coccidioidomycosis were on record in the Los Angeles County Hospital. It is therefore most unlikely that in that endemic area more than the 36 autopsies mentioned above could be available for study, considering the estimated mortality rate of 40 per cent. Stiles and Davis in 1942 found that the sum total of recorded cases of coccidioidomycosis in man did not exceed 790. The total number of autopsies to date could therefore not exceed approximately 316.

In reviewing this group of cases and the literature our attention has been centered upon a number of unsolved problems related to the general pathology of coccidioidomycosis. In the following discussion we hope to present useful

data concerning these problems as they are listed below.

1. The natural reservoir of the etiologic agent and the specific source of human infection.
2. The usual mode of infection of man.
3. The pathogenesis of the lesion in detail, including the mechanism of injury by the organism.
4. The specific factors involved in dissemination of the organisms in the body and the time relationship between the primary inoculation, the disease which follows, and the dissemination of the organism to distal points in the body.
5. The duration and course of *C. immitis* infection and the possibility of more accurate prognosis in the disease.
6. The possibility of spread of the infection to areas distant to the endemic areas through the migration of patients with the disease.

To the study of these problems as our immediate objective may be added the more fundamental objective of our investigations—the expansion of our knowledge and understanding of that general pathologic process, granulomatous inflammation, which is the basis of coccidioidal disease.

The authors of this report did not participate in the actual performance of the autopsies. It therefore seems proper to comment briefly on the materials available. We had for study pertinent gross material, extensive microscopic preparations (even in the absence of gross material), complete summaries of the clinical records of the cases, roentgenograms or photographic duplications thereof, photographs both of the patient and of the lesions, and often complete descriptions of the cultural work done for the identification of the etiologic agent. The biopsy materials, with few exceptions, were accompanied by the essential clinical data and brief descriptions of the operative procedures carried out in obtaining them. The autopsy protocols were detailed and comprehensive, having been prepared strictly according to Army regulations. In general, the records represent exceptionally

TABLE I
SOURCE (HOSPITALS) OF 95 CASES

Hospital	Location	Cases
Santa Ana Air Base	California	8
Beaumont General	El Paso, Texas	11
Brooke General	Fort Sam Houston, Texas	6
Letterman General	San Francisco, California	8
Fitzsimons General	Denver, Colorado	4
Hoff General	Santa Barbara, California	5
Bruns General	Santa Fe, New Mexico	2
Barnes General	Vancouver, Washington	1
Stark General	Charleston, South Carolina	1
Valley Forge General	Phoenixville, Pennsylvania	2
Harmon General	Longview, Texas	1
McCloskey General	Temple, Texas	1
Walter Reed General	Washington, D. C.	2
Newton D. Baker General	Martinsburg, West Virginia	1
Bushnell General	Brigham City, Utah	1
Crile General	Cleveland, Ohio	1
Moore General	Swannanoa, North Carolina	1
Foster General	Jackson, Mississippi	1
Lovell General	Fort Devens, Massachusetts	1
Torney General	Palm Springs, California	1
Tilton General	Fort Dix, New Jersey	1
Lawson General	Atlanta, Georgia	1
Tripler General	Honolulu, Hawaii	1
LaGarde General	New Orleans, Louisiana	1
O'Reilly General	Springfield, Missouri	1
Total Interior General		64
Station Hospital	Stoneman, Pittsburg, Calif.	1
	Camp Van Dorn, Mississippi	1
	Roswell, New Mexico	1
	F. F. McDowell	1
	Camp Ellis, Illinois	1
	March Field, California	2
	Camp Roberts, California	1
	Fort Bragg, North Carolina	1
	Fort Ord, California	1
Receiving Hospital	AAF, San Antonio, Texas	1
Total Interior Station		11
34th General	European Theater	2
67th General	European Theater	1
31st General	Pacific Area	1
93rd General	European Theater	1
179th Station	Panama Canal, Caribbean Area	1
221st Station	Panama Canal, Caribbean Area	1
Total Foreign General and Station		7
7th Field Hospital		1
4th Medical Laboratory	North African and European Theater	1
Total Foreign Miscellaneous		2

TABLE I—(continued)
SOURCE (HOSPITALS) OF 95 CASES

Hospital	Location	Total Cases
Civilian Cases:		
Fitzsimons General		1
Beaumont General		2
Fort Sam Houston Station		1
Letterman General		1
Walter Reed General		1
Mayo Clinic		1
Private Hospital		1
Total Civilian Cases		8
Unknown Sources:		3
Total Unknown Sources		3
Grand Total		95

careful and complete work both on the part of those who performed the autopsies and those who followed the cases clinically.

In order to acquire a general familiarity with the problems presented by our own materials, and thus to determine the possibilities of deriving essential contributions from the study, about half of our cases were analyzed in great detail before any reference was made to previous studies in the field. We next turned to the literature and studied it completely. With the pre-existing picture of coccidioidomycosis thus fixed in our minds, it was then possible to return to the material and proceed with the detailed analysis of the cases with special reference to the less well understood features of the disease. Preliminary tabulations of data relating to specific problems suggested by this review and by the previous studies of the disease were made. In the last analysis it was found desirable to arrange our materials in two major groups, one consisting of cases in which biopsies only were performed, and the other of cases studied at autopsy, as follows.

Total
Number

1. Autopsies:

- a. Biopsies followed by autopsy . . . 16
b. Autopsies without preceding biopsy . 34

2. Biopsies only	45
Total cases	95

The first group proved to be more useful in the formulation of diagnostic criteria for the disease, and the second group in the study of the general pathologic processes involved in this fungus infection.

II

THE HISTORY OF COCCIDIOIDOMYCOSIS

By reviewing the entire literature on the subject of coccidioidomycosis up to March, 1945, we have been able to recognize four fairly sharply defined periods in the history of this disease; they are as follows:

- A. The period of discovery, 1892-1913.
- B. The period of immunologic and epidemiologic development, 1914-1936.
- C. The period of reorientation, 1937-1942.
- D. The period of military infection and dissemination of the disease, 1942-

In order that the important events in the history of coccidioidomycosis may be seen in their proper relationships, the significant contributions of each of these periods will be listed in chronologic order. A complete list of all contributions to the subject up to March,

1945, arranged by years, will be found in the bibliography.

*A. The Period of Discovery,
1892-1913*

1892

Original description of the disease coccidioidomycosis by R. Wernicke,¹ including a brief discussion of the various forms of the parasite responsible for it, characterization of the lesions as "granulation tissue tumors," and classification of the parasite as a protozoan.

1896

Description of the first two cases of coccidioidomycosis occurring on the North American continent by Rixford and Gilchrist.² This includes a detailed study of the parasite and of the pathologic anatomy of the disease. The organism was classified on a preliminary basis as a protozoan; on the recommendation of Stiles, the name *Coccidioides immitis* was assigned to it. Dogs and rabbits were successfully inoculated with the organism.

1900

1. Posadas⁴ published a more comprehensive description of the original case presented in 1892 by Wernicke. Posadas, who originally called attention to the disease while working in Wernicke's laboratory in Buenos Aires, Argentina, reproduced the infection in monkeys and dogs. This is a complete and finished report.

2. Preliminary description of the cultural characteristics of *C. immitis*, representing the first systematic study of this problem, by Ophüls and Moffit.³

1904

Detailed studies of *C. immitis*, including its morphology and cultural characteristics, by Wolbach.⁵

1905

1. A summary of all cases of coccidioidomycosis reported up to this time and a detailed description and comprehensive discussion of the pathologic anatomy, the histology, and the

clinical course of the disease, by Ophüls.⁶ Emphasis in this paper is on the pulmonary portal of entry of the organism and on the primary pulmonary focus of infection. Ophüls reclassified the organism and gave to it the name *Oidium coccidioides*.

2. Detailed report by Ophüls⁷ on the morphology, the life history, and the pathogenicity of *C. immitis* in dogs, rabbits, and guinea pigs. Ophüls thought he recognized a sharp difference between the pathogenic effect of the immature spherule and that of the sporulating spherule; the latter he thought responsible for the nodular epithelioid reaction of the tissues, and former for the suppurative and necrotizing reaction.

1907

A complete survey of all reported cases of coccidioidomycosis and a comparison with cases of blastomycosis, by Hektoen.⁸ Hektoen recognized a primary pulmonary and primary cutaneous form of coccidioidomycosis and emphasized, first, the predilection of the organism for the lymph nodes, and second, the resemblance of the tissue reactions to those in tuberculosis.

1909

Description of the fourth case of *C. immitis* meningitis. This report by Evans¹⁰ describes meningitis unaccompanied by evident infection in other parts of the body—presumably primary coccidioidal meningitis. All previously reported meningeal infections were considered secondary to lesions elsewhere.

1912

First mention of coccidioidal infection in the German literature. This report by von Wasielewski¹¹ deals with cultures of the organism and is largely a review of the American work on the disease.

1913

First report of a case of *C. immitis* infection from Texas. The case was reported as one of blastomycosis, but the organism was

subsequently identified as *C. immitis* by MacNeal and Hjelm.¹² 1915

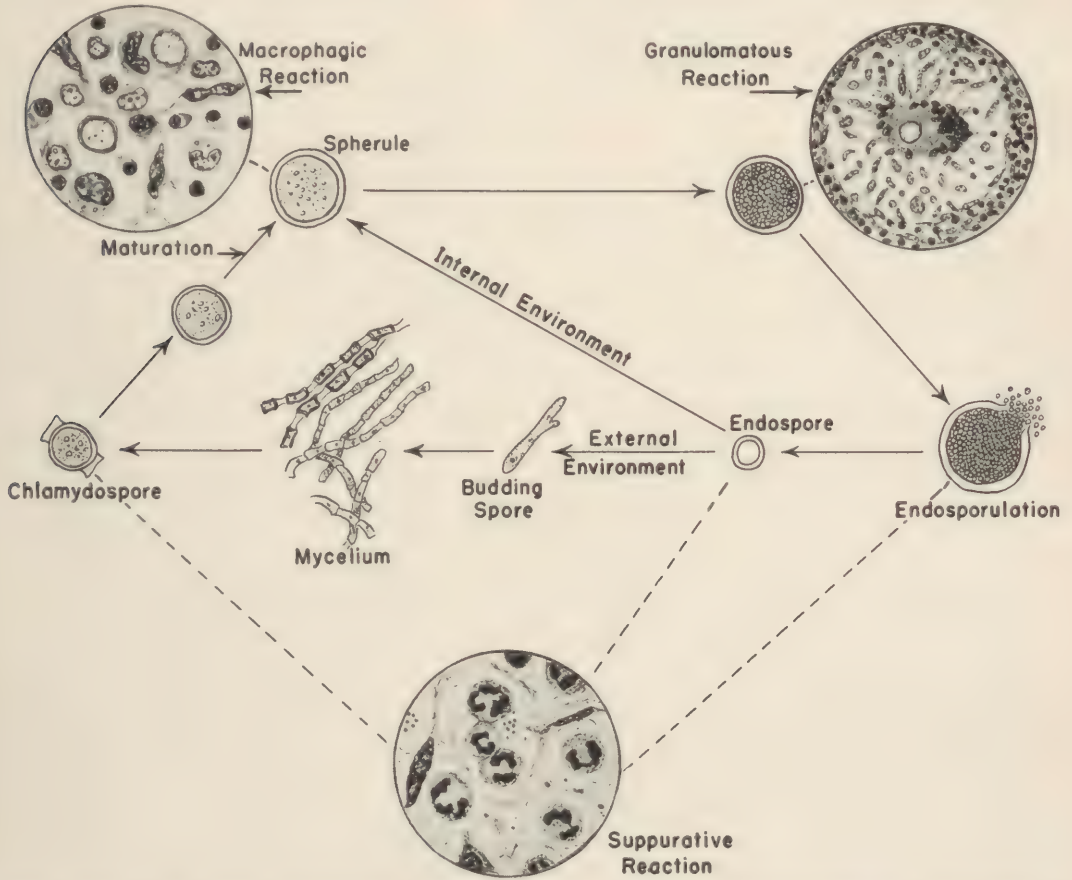
B. The Period of Immunologic and Epidemiologic Development, 1914-1936

1914

1. First studies on immunity demonstrating a specific precipitin reaction in a patient with coccidioidal infection, by Cooke.¹⁴ Cooke

1. The second report dealing with coccidioidomycosis in the European literature. This report by Campiche¹⁶ deals with a case originating in California.

2. A thorough clinical description of coccidioidomycosis by Dickson,¹⁷ with the addition of nine cases to the literature, bringing the total reported cases to 40. Dickson cited the



LIFE CYCLE OF COCCIDIOIDES IMMITIS AND RELATED HISTOLOGICAL RESPONSE

Fig. 1

also tested her patient for a specific skin reaction and for complement-fixing antibodies and agglutinins, but failed to obtain positive results in any of these tests.

2. Discussion of the 24 cases of coccidioidal disease recorded up to this time with an excellent pictorial study of the morphology of the various developmental forms of the parasite, by MacNeal and Taylor.¹⁵

work of Cooke on immunity as the only contribution to date dealing with this aspect of the problem.

1920

Lynch¹⁸ reported the post-mortem study of a case of disseminated coccidioidomycosis in South Carolina. This is the first case observed east of the Mississippi River.

1923

1. Hirsch¹⁹ described a case of coccidioidomycosis in a Pullman porter who contracted the disease in California and migrated to Chicago, where he died. Emphasis was placed on the possibility of spread of the disease by the migration of infected persons.

2. Earliest recorded studies of coccidioidomycosis by x-ray. In this report by Taylor²⁰ attention is called to the similarity of the widespread lesions in the bones and in the lungs to the lesions of disseminated tuberculosis.

1924

First case of "coccidioidomycosis" in Brazil recorded in a study by Gomes and deAssumpcao.²¹

1925

1. Further detailed studies on the general biologic character of *C. immitis* by Bump.²²

2. A comprehensive clinical review of 82 cases of coccidioidomycosis collected from the literature by Riesman and Ahlfeldt.²⁴ Special attention is called in this report to the occurrence of the disease in four women and eight children. Previously the disease was thought to occur almost exclusively in male adults.

3. A report of recovery of *C. immitis* from the blood by culture. This first description of *C. immitis* septicemia is by Montenegro.²³

1926

Ahlfeldt²⁶ demonstrated the possibility of infection of guinea pigs by (1) enforced aspiration of the organism into the lung, (2) feeding infected material, and (3) exposing the animal to an atmosphere infected with the organism. This is one of the earliest experimental studies on the route of infection by *C. immitis*.

1927

1. By using the filtrate of a bouillon culture as antigen, daFonseca and deArea Leao²⁹ clearly demonstrated for the first time that

complement-fixing antibodies occur in the blood of infected patients.

2. DaFonseca and deArea Leao³⁰ demonstrated a specific skin reaction to the filtrate of a bouillon culture of what was believed to be *C. immitis* in a patient with "coccidioidomycosis." The organism under investigation was later (1931, 1932, 1934) proved to be a new species, *Paracoccidioides brasiliensis* (later shown to be a blastomycete) by deAlmeida. (In 1932 deAlmeida also demonstrated that the organism "*Pseudococcidioides mazzai*," introduced by daFonseca from Argentina, is identical with *C. immitis*. De Almeida's work on these organisms has been verified by N. F. Conant and D. J. Davis.)

3. Description of South American blastomycosis by deSouza Campos and deAlmeida³² produced by *Paracoccidioides brasiliensis*, a genuine blastomycete (later named *Blastomyces brasiliensis* by Conant), and distinctly different from *C. immitis*. This report from Sao Paulo in Brazil called attention to a form of granuloma that sharply resembles the granuloma produced by *C. immitis*.

4. Detailed studies of the classification of *C. immitis* in its relation to other pathogenic and non-pathogenic fungi by Castellani.²⁸

5. In association with Benson and d'Andrea, Hirsch^{34,35,36} clearly demonstrated a reliable specific skin and testis reaction to *C. immitis* culture filtrate in both man and guinea pig; this confirmed earlier work and added further emphasis to the possible use of a skin reaction in the diagnosis and study of coccidioidomycosis.

6. Riesman and Ahlfeldt³⁹ summarized the 87 cases reported to date and described one new case, the significant point in which was its origin in New Mexico.

1928

1. Stark and Becker⁴⁷ presented an excellent summary of 89 cases of coccidioidomycosis with extensive clinical and epidemiologic data.

2. Report by Tomlinson and Bancroft^{48,49} of the first laboratory infection by *C. immitis*. This infection occurred in a medical student working with cultures in Weidman's laboratory in Philadelphia.

3. Experimental and clinical investigation of a specific allergic cutaneous reaction in coccidioidal granuloma by Jacobson.⁴⁵ Jacobson recommended the use of the skin test as a diagnostic procedure.

4. Kogoj⁴⁶ experimentally demonstrated a relation between trauma and the localization of *C. immitis* in the skin of animals with general infection. In his experiment a dermatomycosis developed only where the skin had been shaved.

1929

1. Ophüls⁶³ in discussing a paper by Pulford and Larson⁶⁴ called attention to the overwhelming evidence in favor of the lung as the portal of entry of *C. immitis*. He cited the fact that old primary foci may be found in almost all cases of coccidioidal granuloma, and that the pulmonary lesions are always of the greatest clinical and pathologic significance. He discounted the idea that human infection is related in any way to that of the lower animals, stating that animals, like man, get their disease from the soil. Absence of intestinal lesions in coccidioidal granuloma also was emphasized as a characteristic feature of the disease.

2. First description of coccidioidomycosis in six cattle and one sheep slaughtered near Bakersville, California, by Beck.⁵² Beck called attention to the observation of Giltener in which he mentioned having seen coccidioidal granuloma in the bronchial and mediastinal nodes of cattle in 1928.

3. A comparative study of coccidioidal granuloma as it occurs in the United States and a similar disease in Brazil was made by deAlmeida.⁵⁶ He described in great detail the organism responsible for the Brazilian disease (*Paracoccidioides brasiliensis*, later shown to be a blastomycete) and insisted that it is a distinct species quite different from that of North American coccidioidomycosis.

4. Ahlfeldt⁵¹ described two different types of spores in coccidioidomycosis tissues, one staining with osmic acid and the other not. This represents the first observation of spores in the tissues. Ahlfeldt suggested that the two types of spores might represent sexual forms.

5. Publication by Cummins, Smith, and Halliday⁵⁴ of a comprehensive summary of 122 cases of coccidioidomycosis, including excellent tables dealing with incidence, mortality, and duration of the disease, age distribution, nationality and occupation of the patients.

6. Evans and Ball⁵⁸ published from Los Angeles General Hospital, California, a series of 18 autopsies from a total of 50 cases of coccidioidomycosis. This is the first and largest series of autopsies published. The report is especially informative with regard to the relation of pulmonary infection to the other aspects of the disease.

1930

1. The etiologic organism of Brazilian "coccidioidal" granuloma was shown by deAlmeida⁶⁹ to be distinctly different from that producing North American coccidioidomycosis. This work and that which preceded it by the same author and by others established the Brazilian parasite as a distinct species to which the name *Paracoccidioides brasiliensis* has been given. The disease in question was shown to be a blastomycotic, not coccidioidal, granuloma.

2. A brief but complete review of all work on skin reactions in coccidioidomycosis was made by Hirsch and d'Andrea.⁷² In this paper there is described in detail the histologic reaction occurring in the tissues at the site of the skin test. The exudation of fibrin, round cells, fluid, large reticulum cells, and a few neutrophilic and eosinophilic polymorphonuclear leukocytes, without necrosis, was characteristic of the reaction.

3. The first case of coccidioidal meningitis involving the spinal cord and presenting the clinical picture of spinal-cord tumor was reported by Rand.⁷⁹

4. First reference to coccidioidal granuloma in Italy by Radaelli,⁷⁸ who stated that two cases of coccidioidal granuloma had been published in Italy by Jacono.

5. It was suggested by Jaffe⁷⁴ that the large giant cells in the reacting tissues in coccidioidomycosis serve as the host of the organism, remaining intact until the organisms mature. Following maturation and sporulation the

giant cells were thought to break up, with the escape of the spores into the surrounding tissues. Following this, leukocytes were thought to invade the area, thus producing a suppurative lesion. This paper is a very careful and detailed histopathologic study.

1931

1. Beck, Traum, and Harrington⁸¹ review the occurrences of coccidioidal infection in animals, reporting altogether 20 observations to date involving cattle and sheep. This work was the outcome of a survey made in southern California. Only lesions in the bronchial and mediastinal lymph nodes are recorded.

2. An excellent review of the literature by Carter⁸² up to 1931. The author's contribution relates particularly to x-ray diagnosis of pulmonary and bone lesions in coccidioidomycosis. This is the most extensive and comprehensive study made by x-ray to date.

3. First Case reported in China. The patient was a child. This report by Chou and Reiss⁸³ records as a positive autogenous inoculation, accomplished by injection of uninvolved skin of the patient with a culture of its own organisms.

4. Special Bulletin No. 57,⁸⁴ dealing with coccidioidal granuloma, issued by the California State Department of Public Health. In this work are compiled data relating to the occurrence of this disease, not only in California, but elsewhere. The bulletin contains an abundance of source material.

1932

1. First case reported from Mexico, by Perrin.⁹⁷

2. Case originating in Nicaragua reported by Williams in a veteran.¹⁰⁰

3. First instance of isolation of *C. immitis* from the soil. Report by Stewart and Meyer.⁹⁹ Special medium composed of acriflavin, potassium hydrogen phosphate, magnesium sulfate, ammonium chloride, and sodium acetate, used for this purpose.

4. Report of three cases of coccidioidomycosis originating in Texas by Caldwell.⁸⁸ Only

two other cases reported from Texas up to this time.

5. Further studies by deAlmeida⁹² concerning distinction between *Paracoccidioides brasiliensis* and *Coccidioides immitis*, and proving the identity of *Pseudococcidioides mazzai* and *Coccidioides immitis*. The former was first observed in South America by daFonseca and thought to represent a new genus.

1933

First case reported from El Paso, Texas, by L. M. Smith.¹⁰⁷

1934

1. Lutz¹¹⁸ republished a case of "coccidioidal" granuloma published originally in 1908. The observation was made in Brazil. This was said to be the first instance of "coccidioidal" infection in this area. The case was compared carefully with the original case of coccidioidomycosis published by Posadas. This case was subsequently proved to be an instance of blastomycosis caused by *Paracoccidioides brasiliensis*.

2. Third laboratory infection, published by Tomlinson and Bancroft.¹²⁵ (The patient was infected while working with *C. immitis* at the University of Nebraska.)

3. Ciferri and Radaelli¹¹³ succeeded in propagating the spherules of *C. immitis* in the absence of hyphae in gelatin cultures. These workers suggested the possibility of conjugation of two or even three spherules when the organism is grown in appropriate cultures.

4. Third Italian case observed in Naples, by Radaelli and Ciferri.¹²¹ These workers stated that the two other cases were reported by Poeri and Jacono. The Italian organisms proved to be much less pathogenic for both man and animals than the American strain of *C. immitis*. (Conant has studied the Italian cultures and states that there is no doubt of their identity with *C. immitis*.)

5. A detailed study of fungus infections of bone, including infection by *C. immitis*, was published by Carter.¹¹¹ This is an x-ray study supplementing his previous contribution in this field.

6. A careful study of the morphology of

a variety of fungi including *C. immitis*, with special reference to the formation of radiating clublike bodies by the capsules of the spherules of *C. immitis* and by other forms of other fungi, was made by deAlmeida.¹¹⁷ He suggested that these bodies are not products of the environment of the parasite, but are part of the parasite itself.

7. Publication of an especially good comparative study of *Cryptococcus hominis*, *Blastomyces dermatitidis*, and *Coccidioides immitis* by Benham.¹¹⁰

8. Publication of the first case in Louisiana and the second case east of the Mississippi River, by McDonald.¹¹⁹

1935

1. First case reported from San Antonio, Texas. The patient was a Mexican, native to Texas. Report by Lehman and Pipkin.¹²⁸

2. Fennel¹²⁷ reported the second case from Hawaii, the patient in this case being a native Hawaiian. He suggested that the infection may have developed from the handling of California fruit products.

1936

1. Final clarification of the whole problem of North American and Brazilian "coccidioid" granuloma by Jordon and Weidman.¹³⁴ In this paper a clear distinction is drawn between the Brazilian and the North American organism, *Paracoccidioides brasiliensis* and *Coccidioides immitis*, respectively. The name Almeida's disease is suggested for the Brazilian "coccidioid" granuloma, which is now considered to be a form of blastomycosis.

2. Description of 14 cases of coccidioid meningitis by Abbott and Cutler.¹³⁰ This paper also contains important statistical data relating to coccidioidomycosis as observed in the Los Angeles General Hospital, California. It is stated that in 12,000 autopsies 36 of coccidioidomycosis had been studied. This is the largest series of autopsies mentioned in the literature to this date, but it has not been published.

3. First case published from Kansas, by Van Cleve.¹³⁷ The patient was infected pre-

sumably by the handling of chicken food made from the meat of condemned cattle. The primary lesion occurred on the finger.

C. The Period of Reorientation—Discovery of the Etiologic Relationship between San Joaquin Valley Fever, with its Characteristic Accompaniment, Erythema Nodosum or the "Bumps," and Coccidioid Granuloma, Thus Disclosing the Primary or Early Phase of the Entity Coccidioidomycosis, 1937-1942

1937

1. Report from the California Department of Public Health¹³⁹ summarizing work on coccidioid granuloma in California for the years 1934 and 1935, including report by Dr. Joe Smith of Bakersfield, California, in which is described pulmonary or primary coccidioidomycosis. In this report are summarized 450 cases of coccidioid infection in California, 224 of which were fatal, thus establishing the mortality rate at about 46 per cent.

2. First report by Dickson¹⁴¹ describing a newly recognized entity, pulmonary or primary coccidioidomycosis, as he had observed it in a laboratory infection. It was in this connection that Dickson made the suggestion that coccidioid granuloma was most likely merely the advanced stage of a primary pulmonary infection, and that the lung is the usual portal of entry for *C. immitis*. It was at this time also that Dickson¹⁴⁰ established the identity of "valley fever" of the San Joaquin Valley and primary pulmonary coccidioid infection.

In 1934 Gifford had recovered *C. immitis* from the lung in one of her cases of "valley fever" with erythema nodosum. The record of this case was shown to Dickson in 1936 by Gifford. Gifford's observation seems to have been the first objective demonstration of the etiologic relationship between "valley fever" and coccidioid infection. This observation and Dickson's own study of his laboratory infection formed the basis for the subsequent work which led to unquestioned recognition of the identity of coccidioid granuloma and San Joaquin Valley fever.

3. Demonstration by Miller¹⁴⁴ of various

forms of pulmonary coccidioidomycosis, including (1) the development of caseous nodules in the lung, (2) pulmonary cavity formation, (3) caseating granulomatous pneumonia with multiple cavities, (4) bronchial granulomatous scarring. Miller called attention at this time to an observation that old fibrous lesions due to coccidioidomycosis may persist for years and then become active and give rise to dissemination of the organism to other parts of the body.

1938

1. Publication of the biennial report of the Kern County, California, Department of Public Health, in which Gifford¹⁵⁰ records her observation of 1934 that *C. immitis* is recoverable from cases of "valley fever" with erythema nodosum. As noted above, this observation had previously been shared with Dickson.

2. Report of the first large-scale study of intradermal skin reaction to products of *C. immitis*. This work was carried out in California by Hurwitz, Young, and Eddie,¹⁵¹ and involved tests of 449 individuals.

3. Further studies on the morphology and biology of *C. immitis* demonstrating the formation of spherules with their maturation and endospore formation from chlamydo-spores in *in vitro* cultures, by Lack.¹⁵²

4. Publication of the only recorded instance of valvular endocarditis in coccidioidomycosis, by Epstein.¹⁴⁹

5. Report of further studies of primary coccidioidomycosis by Dickson and Gifford,¹⁴⁸ and by Dickson,¹⁴⁷ indicating further the relationship between "valley fever" and coccidioid granuloma.

6. Demonstration by Wooly¹⁵⁶ of *C. immitis* in the sputum of patients being treated for pulmonary tuberculosis in Arizona. All cases with positive sputum were proved to be instances of coccidioidomycosis, and not tuberculosis.

1939

1. Demonstration by Kessel¹⁶⁴ of the spe-

cificity of the coccidioidin test and its independence of the tuberculin reaction.

2. Demonstration by Cox and Smith¹⁵⁸ of arrested pulmonary coccidioid granuloma. Four cases were described in which old, encapsulated, caseous, partially calcified coccidioid lesions harboring typical organisms were found. Similar quiescent lesions were demonstrated in experimental animals. Sporulating organisms were found in arrested human lesions of from 2 to 15 years' duration.

3. First case reported in a native of Tucson, Arizona, by Storts.¹⁶⁸ This was a case of fatal meningitis, clinically resembling a brain tumor, in a child aged four. No other coccidioid lesions were found in this child except a hard nodule in the lung, in which typical organisms were found. This case confirms the observation of Cox and Smith relative to the dissemination of virulent organisms from an old, presumably inactive lesion in the lung.

4. Faber, Smith, and Dickson¹⁵⁹ made an extensive report on the relationship between erythema nodosum and primary pulmonary coccidioidomycosis or "valley fever." A detailed description of cases of "valley fever" with erythema nodosum was made, and it was shown that the infection with *C. immitis* accompanied by erythema nodosum gives rise to complete immunity to further coccidioid disease. It was observed that generalized granuloma developed in only one of 700 cases of primary infection with erythema nodosum.

5. Further studies on the relation between erythema nodosum and infection by *C. immitis* by Thorner.¹⁶⁹

6. Demonstration by Phillips¹⁶⁶ of the existence of coccidioid infection in Phoenix, Arizona, through the procedure of skin testing.

7. Confirmation of the existence of coccidioid infection in Arizona by Brown,¹⁵⁷ who demonstrated positive skin reactions in cases of erythema nodosum occurring in this area.

1940

1. Report of an epidemiologic survey of the occurrence of coccidioidomycosis with ery-

thema nodosum in Kern and Tulare Counties of southern California. In this report Smith¹⁷⁵ adds further support for a specific relationship between *C. immitis* infection and the erythema nodosum endemic in that area.

2. Standardization of preparations of coccidioidin for use in skin testing for coccidioid infection, by Stewart and Kimura.¹⁷⁶

3. Confirmation of the existence of coccidioid infection, in southern Arizona, by Mills and Farness,¹⁷³ who recorded the occurrence of ten or more cases of coccidioid disease in that area. The existence of this focus was first indicated by Aronson, who found positive coccidioidin skin reactions in Prima Indians.

4. Development of methods for the study of early primary lesions in the experimental animal, by Cronkite and Lack.¹⁷⁰

1941

1. Report of a careful study of primary pulmonary coccidioidomycosis in an epidemic involving a group of 14 students who acquired the infection simultaneously while on a biology field trip in an endemic area. This report by Powers and Starks¹⁸¹ is based on x-ray studies, and for the first time records the changes that occur in the lungs in the course of the development and recession of the pulmonary reactions to *C. immitis*. Correlation of these findings with those of previous studies of "valley fever," erythema nodosum, etc., further confirmed the identity of primary coccidioidomycosis of the lung and these disorders.

2. Careful x-ray study of cavity formation in primary pulmonary coccidioidomycosis by Winn.¹⁸⁵

3. Demonstration by Thorner¹⁸⁴ of a very low ratio between the incidence of "valley fever" and positive coccidioidin reactions in 267 school children in Kern County, California, indicating that "valley fever" is a very benign and perhaps universal infection in that area.

1942

1. The isolation of *C. immitis* from the soil and from rodents in San Carlos, Arizona,

by Emmons.¹⁹⁶ In the area studied there was no record of coccidioidomycosis among the inhabitants, but Aronson previously had found that many of them exhibited positive coccidioidin skin reactions. Emmons suggested in his paper that wild animals may be the natural reservoir for *C. immitis*.

2. Study of an epidemic of coccidioidomycosis of the primary pulmonary type in a group of students, by Davis, Smith, and Smith.¹⁹³ This is a careful clinical study of the same group of cases studied roentgenologically by Powers and Starks, as previously noted.

3. Aronson and Gallagher¹⁸⁶ determined the sensitivity to coccidioidin of 680 boys in an Eastern preparatory school, while studying reactions to the tuberculin test. Seventeen positive reactors to coccidioidin were found, five of whom had calcified nodules in the lung. Twelve failed to react to tuberculin. This experiment centered attention upon the possibility that focal calcification in the lung ordinarily attributed to tuberculosis might be the result of coccidioid infection.

4. Aronson, Saylor, and Parr¹⁸⁷ demonstrated conclusively that calcified nodules in the lung occur in a high percentage of persons with positive coccidioidin and negative tuberculin reactions. This confirmed previous observations that calcified nodules in the lung arise from previous and healed infection with *C. immitis*.

5. Stiles and Davis²⁰⁶ found that sheep, cattle, dogs, and wild rodents not infrequently are infected in areas where coccidioidomycosis is endemic in man.

6. Schenken and Palik²⁰¹ made a careful analysis of all the reported cases of coccidioidomycosis and concluded that only 17 cases on record could be proved conclusively to have occurred independent of contact with California. The sources of infection of 12 of the 17 non-California cases were found to be Texas, Arizona, and New Mexico. These studies indicate therefore that up to this time only five cases of conclusively proved coccidioidomycosis had occurred outside of California, Texas, Arizona, and New Mexico. The criteria used in this study are extremely rigid.

7. Winn and Johnson²⁰⁹ in concluding a report of a study by x-ray of primary coccidioidomycosis made the following significant prediction: "The coming of large numbers of uninfected persons, especially military personnel, into the inland California valleys and certain parts of Arizona and Texas will result in a proportional increase in the incidence of coccidioidomycosis." The experiences of the armed forces during the following four years fully justified this prediction.

8. Experimental inoculation of mice intranasally and intraperitoneally with *C. immitis* by Taeger and Liebow.²⁰⁷ This report deals especially with the chemotactic properties of different forms of *C. immitis* as they appear in the tissues.

9. Further confirmation of the occurrence of coccidioidomycosis in areas of Texas extensively used for military purposes. These reports are by Caldwell,¹⁹¹ Smith,²⁰⁵ Martin,¹⁹⁸ and Schulze.²⁰²

10. Discovery by Ashburn and Emmons¹⁸⁸ of a form of granulomatous disease in wild rodents produced by *Haplosporangium parvum* and sometimes associated with coccidioidomycosis. This observation added a new problem to the epidemiology of coccidioidomycosis.

D. The Period of Military Infection and Dissemination of the Disease, 1942-

1942

First report from military installations in California dealing with coccidioidomycosis. This report by Shelton²⁰³ records the development of positive coccidioidin reactions in troops brought into that area within the first three months of residence. Several cases of coccidioidomycosis developed in Camp Roberts within the three-months period, although the area in which the camp was situated was not known to be one of endemic infection.

1943

1. Further studies of coccidioidomycosis in wild rodents, by Emmons.²¹² Again he suggested the possibility of determining the extent of endemic areas of coccidioidomycosis through the examination of wild animals.

2. Report of studies of the chemical composition of a specific polysaccharide found in culture filtrates of *C. immitis*, by Hassid, Baker, and McCready.²¹⁴ This polysaccharide was found to give a positive skin reaction and to act as specific antigen for the precipitin reaction, but not for the complement-fixation reaction.

3. An excellent review of the morphology, taxonomy, and distribution of *C. immitis*, published by Baker, Mrak, and Smith.²¹⁰ This paper also contains an excellent and comprehensive review of all previous work done on the general biology of this organism.

4. The second report on the occurrence of coccidioidomycosis in military installations, by Goldstein and Louie.²¹³ This paper describes an epidemic of 75 cases of coccidioidomycosis, which occurred in a body of troops on detail in an endemic area. The report is important because of its contribution relating to primary pulmonary infection. Up to the time of publication of the report the granulomatous or disseminated form of the disease had developed in only one of the 75 patients involved.

1944

1. Report by Colburn²²⁰ on the x-ray findings in the epidemic coccidioidomycosis among Army personnel, described by Goldstein and Louie. This is the fourth report on the occurrence of coccidioidomycosis in military personnel. It is important from the point of view of primary pulmonary infection.

2. A follow-up study by Goldstein and McDonald²²² of the 75 cases recorded in the epidemic described in the two preceding papers. This report contains excellent clinical data relating to primary pulmonary infection and records ten additional cases in Army personnel. In all of these the disease was contracted near the California-Arizona border, an area in which coccidioidomycosis was not at that time known to be endemic.

3. Publication by McKenney, Traum, and Bonestell²²⁶ of a report on the occurrence of coccidioidomycosis in a mountain gorilla in the Zoölogical Museum at San Diego. It is recorded in this paper that other anthropoids,

American monkeys, dying in this same museum, had been found to be infected by *C. immitis*.

4. The fifth report of coccidioidomycosis in military personnel, by Quill and Burch.²²⁹ This report describes the disease in Texas installations and reviews all of the previously described cases originating in Texas. They are listed by location as follows:

Cases

San Angelo	4
Dallas	7
El Paso	5
San Antonio (civilian)	6

5. Brief summary of experiences with coccidioidomycosis in the Western Flying Training Command of the Army, by Lee.²²⁴ This is the sixth report dealing with coccidioidomycosis in military installations.

6. The seventh report on coccidioidomycosis in Army installations, by Cheney and Denenholz.²¹⁸ This report presents a clinical study of 14 cases of coccidioidomycosis which occurred at Hammond General Hospital in California. The material presented is excellent from the clinical, immunologic, and bacteriologic points of view. Of the 14 cases, ten were of the primary benign pulmonary type, and four of the disseminated form.

7. Detailed report of studies on coccidioidomycosis carried out for the Commission on Epidemiological Survey, Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army, Preventive Medicine Division, Office of the Surgeon General.²¹⁹ This is an unpublished report covering a comprehensive study of coccidioidomycosis occurring at Minter, Gardner, Lemoore, and Merced airfields in California.

8. Publication of a syllabus on coccidioidomycosis by Lee and Nixon, with extensive roentgenograms by Jamison,²²³ for the use of the medical officers of the Army Air Forces Western Flying Training Command. This syllabus, originally prepared and distributed in 1942, describes the coccidioidomycosis control program in the Western Flying Training Command of the Army Air Forces and also presents a brief but complete description of

coccidioidomycosis from the clinical and roentgenologic points of view.

1945

1. The eighth report on coccidioidomycosis occurring in military personnel and the first report published from the Army Institute of Pathology dealing with the pathologic anatomy of coccidioidomycosis. This report by Schlumberger²³⁶ describes 13 cases of coccidioidomycotic meningitis; these are included in the 95 cases of this present report.

2. The ninth report of coccidioidomycosis in Army personnel, by Bass.²³¹ This is a report of four cases from the Bruns General Hospital, Santa Fe, New Mexico; it deals especially with roentgenologic diagnosis of the disease.

3. The tenth report of coccidioidomycosis in Army personnel, by McCracken.²³⁵ This study deals with four cases of coccidioidomycosis in soldiers at Fort Bragg, North Carolina. Three of the patients had trained in California and one in Arizona. The disease appeared in the three patients from California while they were en route to Fort Bragg. The disseminated form of the disease developed in only one case, some months after arrival at Fort Bragg.

4. The eleventh report of coccidioidomycosis in Army personnel by Kunstadter and Pendergrass,²³⁴ from Ashford General Hospital, West Virginia. In this paper attention is called to the occurrence of an arrested form of Coccidioidomycosis, characterized by the presence of multiple or solitary caseous nodules in the lung. In the case reported there was no active coccidioidomycosis. The quiescent pulmonary lesions were found incidentally in the course of an autopsy following death from an accident.

III

DISTRIBUTION OF CASES

A. Origin of the Cases

The several sources of materials made use of in this study are shown in Table I. It is important to note that this table gives only in a

general way the geographic location in which the infections occurred, and in some instances is no indication whatever of the origin of the infection. This is especially true when the cases were reported from hospitals situated outside of the United States. It will be noted from Table I that in nine cases the disease developed in apparently normal individuals after they had left this country for active duty in foreign theaters of war. The table also indicates that dissemination of the infection within this country may be in progress through the movements

TABLE II
GEOGRAPHIC SITE OF ORIGIN

	Total Number
Arizona	24
California	37
California and/or Arizona	4
California and/or Texas	1
Texas	12
New Mexico	1
Colorado	1
Utah	1
Oregon	1
Missouri	1 (?)
Unknown origin	12
Total	95

of subclinically infected persons from one Army installation to another. This is shown specifically by the occurrence of four cases of coccidioidomycosis at Fort Bragg, North Carolina, in an area where the disease had never before been seen. In this group of cases, reported by McCracken, three of the patients actually were suffering from active coccidioidomycosis on arrival at Fort Bragg from California. The fourth had been in Arizona, but the disease appeared only after several months of residence at Fort Bragg. Whether this experience is an indication of what may be expected on a far greater scale in the future remains, of course, to be seen.

It was to be expected that the utilization of the Southwest for military training purposes would increase the incidence of coccidioidomycosis in the endemic areas. While, of course,

the clinical records of the Army medical department will give a far more accurate picture of the degree and extent of this increase in coccidioidomycosis, our study of a small group of 95 cases, 50 of which were fatal and all of which were of the disseminated type, gives a clear indication of what occurred. The origins of the 95 infections with *C. immitis* reported here are summarized in Table II.

These data do not provide a satisfactory basis for discussion but it is rather interesting that the number of cases in this series originating in Texas is slightly in excess of the total number of cases of coccidioidomycosis reported as having occurred in that state up to October 1942. It will be recalled that the disease was not recognized in Texas until Caldwell published his paper in 1932 (two of the five cases he reported had, according to him, been published previously, but he does not give a date of publication.) The largest group of cases is reported from California, which is in harmony with the prevalence of the disease in that area. The relatively large number from Arizona is interesting in view of the fact that the disease was not recognized in that state until 1938, when Woolly observed the first case in Tucson. This was followed in 1939 by the demonstration by Phillips of a high incidence of positive coccidioidin skin tests in the region around Phoenix. Another significant observation made the same year by Brown was the occurrence of a number of cases of erythema nodosum in this same area.

The data in this series of 95 cases relating to the age and sex incidence of the disease are valueless in view of the highly selective type of material with which we are concerned. Most of the cases were among the age groups of greatest numerical strength in the armed forces. In only one instance was the infection present in a woman, the wife of a soldier.

The occupational factor, which has appeared to be of significance in other series of cases, was almost impossible to assess. The data on branch of service and military rank, the only suggestions of occupational status in the protocols, were meaningless.

The place of birth was unknown in more

than a third of the cases and added no helpful information in those in which it was known.

Exclusive of the geographic sites of origin, only the figures on the race of patients with disseminated coccidioidomycosis appear significant.

B. Race of the Patients

Table III summarizes the data relating to the factor of race in the development of the disseminated form of coccidioidomycosis. There is a common belief, indicated by the widespread publication of statements to this effect, that dark-skinned peoples are more susceptible than white to coccidioidal infection, particularly to the disseminated form of the disease. Our data give some support to the general opinion that colored Americans are more apt to develop the disseminated form of coccidioidomycosis than are other races, but the significance of the data is debatable. It may be added that insofar as the general clinical and pathologic-anatomic character of the disease is concerned there are no appreciable differences between the infections in colored and white Americans.

IV

CLINICAL FEATURES

A. Data from Analysis of 45 Surviving Cases of Coccidioidomycosis Diagnosed by Biopsy of Disseminated Lesions

The diagnosis of coccidioidomycosis, even of the extensively disseminated type, is not an easy matter, because of the resemblance of the lesions and of the disease as a whole to a variety of chronic granulomatous infections. The three most important diseases with which it may be confused are tuberculosis, blastomycosis, and actinomycosis. In areas where coccidioidomycosis is endemic, its presence is always suspected when a patient has widely disseminated suppurative lesions involving the bone and the subcutaneous tissues. Outside of endemic localities such processes rarely indicate any one etiologic entity, and the diagnosis is therefore not made until the specific organisms are demonstrated in exudate from the

open lesion by cultural examination or in histologic preparations of excised tissue. The compilation of the data from the 45 cases of disseminated coccidioidomycosis diagnosed by biopsy will therefore serve a useful purpose for those who are concerned with the diagnosis of the disease.

In considering the figures pertaining to this group, it is important to keep in mind that all the cases presented an advanced stage of the coccidioidomycotic process and thus are es-

TABLE III
THE RACE FACTOR IN 95 CASES

	Total Number
White, American	37
Colored, American	48
Mexican	2
Filipino	1
American Indian	1
Oriental (Chinese)	1
Unknown race	5
Total	95

entially like those studied at autopsy. They represent, nevertheless, what might be regarded as an intermediate stage in the development of coccidioidal infection, and hence deserve special study, since data obtained from this group throw light upon the natural course of the disease. Furthermore, some of these cases have come under observation so early that it is reasonable to consider them primary infections. The study of these cases helps to determine more accurately the portal of entry of *C. immitis*. In contrast to those of short duration, there are cases in this group which, because of the long duration, represent unquestioned reinfection of internal original. A study of the latter group furnishes information on the resistance of the individual to coccidioidal infection and the process of healing of the foci of primary inoculation.

In accordance with the general mortality statistics, it is to be expected that approximately 40 per cent of this group of cases in which biopsy has been performed will be fatal.

TABLE IV
DIAGNOSIS BY BIOPSY

Lesion Excised	Organisms Demonstrated		Lesions in Other Organs		Serological Reactions		Duration Days Cases		No. of Cases
Skin and subcutaneous tissues	In sections	16	Lung	3	Coccidioidin	2	1- 30	—	17
	By culture	1	Nodes	1	Complement	1	31- 60	4	
	By an. inoc.	3			Precipitin	1	61- 90	4	
	Not demons.	1			Sed. Rate+	2	91-120	3	
							121-150	1	
							151-180	1	
							181-210	—	
							301	1	
							Unknown	3	
Lymph nodes (+skin: 4)	In sections	10	Lung	3	Coccidioidin	2	1- 30	1	10
	By culture	—	Skin	4	Complement	1	31- 60	2	
	By an. inoc.	—			Precipitin	1	61- 90	—	
					Sed. Rate+	1	91-120	—	
							121-150	1	
							151-180	1	
							181-210	1	
							240	1	
							400	1	
							Unknown	2	
Bones (+skin: 1) (+node: 1) (+joint: 1)	In sections	10	Lung	1	Coccidioidin	1	1- 30	1	10
	By culture	—	Skin and Sub-		Complement	1	31- 60	2	
	By an. inoc.	1	cut. Tissue	1	Precipitin	—	61- 90	2	
			Joint, knee	1	Sed. Rate+	—	91-120	—	
							121-150	—	
							151-180	—	
							181-210	2	
							211-240	—	
							241-270	1	
							480	1	
Lung	In sections	3			Coccidioidin	1	1- 30	1	5
	By culture	—			Complement	—	31- 60	—	
	By an. inoc.	—			Precipitin	—	61- 90	1	
					Sed. Rate+	1	91-120	—	
							1080	1	
Peritoneum							1175	1	
							3240	1	
	In sections	1	Retroperito-		Coccidioidin	—	Unknown	1	
			neal nodes	1	Complement	—			
					Precipitin	—			
Meninges (+node: 1)					Sed. Rate+	—			2
	In sections	1	Nodes	1	Coccidioidin	—	360-	1	
	By culture	1					Unknown	1	
	By an. inoc.	1							

In Table IV are summarized the essential data available on the 45 cases of coccidioidomycosis on record with survival to the present time.

Table IV furnishes useful information relating to the diagnosis of the disease by biopsy and to the study of the general character of disseminated coccidioidomycosis, as summarized in the following paragraphs.

1. *Duration of the disease until time of biopsy:* The shortest period over which symptoms had been observed prior to biopsy was five days, the longest 3,240 days. Twenty-nine (68 per cent) of the cases had a maximum duration of 210 days or less with an average of 87 days. In only 8 cases was there definite information that symptoms had been present longer than 210 days.

2. *Distribution of lesions excised for diagnosis:*

	Cases
Skin and subcutaneous tissues only	17
Lymph nodes (with skin in 4 cases)	10
Bones (with skin, joint tissues, and lymph nodes in one case)	10
Lungs (lobectomy or thoracotomy)	5
Peritoneum (omentum)	1
Meninges (laminectomy or craniotomy; with lymph nodes in one case)	2

In all 17 of the cases in which the skin and subcutaneous tissues were excised the skin lesions consisted of ulcerated or non-ulcerated nodules or of indurated sinuses leading from deeply situated lesions, often in the bone. On exploration, lesions in the bone were usually found to be large, destructive, and suppurating processes involving either the medullary cavity or the cortex with the overlying periosteum. They were found in a great variety of bones, as indicated in Tables IV and XIII.

The lymph nodes excised for diagnosis were sometimes secondarily related to regional superficial lesions, but most often they were involved in the course of dissemination of the organisms by way of the blood.

The biopsied lung lesions consisted of solitary foci of granulomatous tissue, which in roentgenograms bore striking resemblance to genuine neoplasms of the lung. The lesions were excised because of the diagnosis, and it was surprising to find them to be old, partially healed coccidioidomycotic lesions. The meningeal biopsies were performed for suspected

brain tumor in one instance and cord neoplasm in the other.

3. *Demonstration of the organisms in excised tissues:* The finding of typical spherical forms of *C. immitis* in the tissues is the critical diagnostic point; without this the diagnosis of coccidioidomycosis cannot be made unless the fungus is obtained in culture or by inoculation into the experimental animal. The histologic character of the lesion varies greatly and is not specific for *C. immitis*. The record of demonstration of the organism in the tissues by cultures and by inoculation in this series of cases is as follows:

	Cases
Organisms demonstrated in section	41
Organisms demonstrated by culture	3
Organisms demonstrated by animal inoculation	5
Organisms not demonstrated	1

In the last case just cited the diagnosis was based on the combination of a specific immune reaction, a typical clinical history, and a study of the histologic reaction. Ordinarily there is no difficulty in the recognition of the organisms in tissue sections. In the long-standing chronic lesion, however, the organisms tend to be scarce and often show extensive degenerative alteration which makes their identification uncertain and sometimes impossible. In such cases cultures and animal inoculations are required. The reliability of the study of excised tissues for diagnosis is indicated by demonstration of the etiologic agent in the tissue in 41 of the 45 cases studied.

4. *Distribution of lesions in the biopsied cases:* Granulomatous lesions were demonstrated regularly at exploration for diagnosis in the 37 cases with superficial manifestations. Lesions were most consistently found in the lung, an observation which tends to support Ophüls' very early contention that the lungs are the portal of entry in the vast majority of cases. The primary lesion in this tissue, for many years referred to as "coccidioid granuloma," serves as the source for either early or late dissemination of the organisms. The significance and the importance of the primary pulmonary lesion will be discussed in a subse-

quent section on the pathologic anatomy of this disease.

5. *Immunologic and serologic data:* This group of data is not sufficiently complete to lend itself to discussion. In brief, the coccidioidin skin test was positive in six of the cases; complement-fixation was obtained in three; the precipitin reaction was positive in significant dilution in two cases; and the sedimentation rate was elevated in five. Data of this kind are important in the diagnosis when the morphologic and cultural identification of suspected organisms is uncertain.

B. *Clinical Data from 95 Cases (50 Fatal and 45 Surviving) of Disseminated Coccidioidomycosis*

The clinical data from the entire series of 95 cases have been treated as a whole because all actually belong to the same category, being

TABLE V
DURATION OF 50 FATAL CASES OF DISSEMINATED COCCIDIOIDOMYCOSIS

	Total Number
1-30 days	2
31-60 days	6
61-90 days	9
91-120 days	7
121-150 days	5
151-180 days	5
181-210 days	2
211-240 days	3
241-270 days	0
271-300 days	3
301-330 days	2
451-480 days	2
Unknown duration	4
Total	50

characterized by either a limited or widespread dissemination of lesions throughout the body. Only the most significant of the clinical manifestations have been selected and catalogued. Particular attention has been paid to the initiating signs and symptoms because they obviously contribute to an understanding of the early stages in the pathogenesis of the disease

and particularly of the portal of entry of the organisms. In view of the fact that only slightly over half of the cases covered in this report were studied at autopsy, a careful survey of the character and distribution of the lesions as ascertained by roentgenologic and other clinical techniques has been made. The roentgenologic findings, particularly those in the lungs, have proved most helpful in the study of the disease in our cases since repeated previous roentgenologic studies have provided good leads toward an understanding of the pathogenesis and course of development of these lesions. The necessarily limited value of the clinical findings is enhanced by the correlation of data obtained in the post-mortem studies of the fatal cases.

1. *The duration of the disease in 50 fatal cases of coccidioidomycosis:* The shortest course of the disease in the 50 fatal cases was found to be 25 days, the longest 467 days. Thirty-six, or over 70 per cent, ran a course of 210 days or less; and the average duration was 104 days (100 days taking the median). If, for purposes of studying the character, time, and extent of dissemination of the lesions, etc., the figures for the biopsied cases and those for the fatal cases be combined (an entirely justifiable procedure in view of the disseminative character of the disease in both groups of cases), the average duration of the disease in the combined series of 65 cases running a course of 210 days or less is found to be 95 days. The figures are represented in the following summary.

In 29 cases in which biopsy succeeded onset within 210 days or less, the average duration of the disease processes in surviving patients was 87 days.

In 36 fatal cases in which death occurred in 210 days or less, the average duration of the disease processes in patients dying of the disease was 104 days.

In 65 cases of 210 days duration or less, the average duration of the disease processes was 95 days.

It is necessary to emphasize that the average duration figure of 95 days in the 65 cases of 210 days duration or less refers to the dis-

ease processes and has no meaning with regard to the average length of the course of the disease in patients recovering from or dying of coccidioidomycosis. The figure is therefore useful only in connection with a study of the development of the pathologic processes concerned in the disease entity, as suggested above.

TABLE VI

INITIATING SIGNS AND SYMPTOMS IN 95 CASES (50 FATAL AND 45 SURVIVING) OF DISSEMINATED COCCIDIOIDOMYCOSIS

		Total Number
Pain:		50
Chest	21	
Headache	11	
Joints	5	
Back	4	
Abdomen	4	
Generalized ache	3	
Bones	2	
Swelling:		27
Cutaneous nodule	11	
Subcutaneous mass	7	
Bone	6	
Joint	2	
Abdomen	1	
Cough		30
Fever		23
Cold in chest		11
Chills		8
Malaise		6
Weakness and fatigue		6
Hemorrhagic sputum		5
Nausea and vomiting		5
Hoarseness		3
Stiff neck		3
Sweating		3
Ulcer, chronic (sinus) of skin		3
Weight loss		3
Anorexia		2
Diplopia		2
Dyspnea		2
Sore throat		2
Confusion, mental		1
Dizziness		1
Drowsiness		1
Hemorrhage, pulmonary		1
Jaundice		1
Photophobia		1
Staggering gait		1
Urinary retention		1

2. *The initiating signs and symptoms in 95 cases of disseminated coccidioidomycosis:* The signs and symptoms most often present at the onset of this disease point definitely to a lesion in the chest. The patient usually complained of cough, chest pain, and chest cold. Next in frequency were symptoms such as chills, fever, malaise, and anorexia. In about a third of the cases these two groups of signs and symptoms were combined with a swelling situated in the skin or subcutaneous tissue. These data, especially when derived from the cases of short duration, indicate definitely that the portal of entry of the organism is the respiratory tract. Furthermore, they show also that dissemination of the organisms into distal portions of the body may occur while the primary pulmonary lesion is in its earliest stages of development or is rapidly extending to involve the lung as a whole. This observation is supported by repeated roentgen examinations of the chest, especially in the cases of shortest duration. The initiating signs and symptoms in the 95 cases under consideration and their frequency of occurrence are shown in Table VI.

3. *General symptomatology:* The list of symptoms and signs making up Table VII includes and supplements the data in Table VI.

Although this tabulation gives some idea of the general clinical effect of coccidioidal infection, the data are not sufficiently abundant or comprehensive to justify analysis. The figures in this table are not so significant as those in Table VI, the initiating symptoms, which were carefully determined in all cases of the series. Nevertheless, the general symptomatology, as pictured by this accumulation of data, does indicate the existence of significant infection in the lungs in a majority of the cases.

The signs and symptoms referable directly to the various disseminated lesions, individually or in groups, are not included in this table of general symptomatology. With the exception of those pointing toward disease in the lungs, the most prominent group of signs and symptoms indicate intracranial involvement, especially of the meninges. This is not surprising in view of the relatively large number of cases

of coccidioidal meningitis encountered in this study.

Especially worthy of emphasis is the almost complete absence of erythema nodosum in this group of cases. This cutaneous manifestation of the disease has been shown by the California workers to be frequent in cases of

TABLE VII
GENERAL SYMPTOMS AND SIGNS IN 95 CASES (50 FATAL
AND 45 SURVIVING) OF DISSEMINATED
COCCIDIOIDOMYCOSIS

	Total Number
Pain:	
Chest	30
Headache	29
Joints	16
Back	13
Abdomen	2
Fever	50
Cough	33
Weight loss	32
Stiff neck	23
Weakness, malaise, fatigue	19
Drowsiness, coma	17
Nausea and vomiting	15
Paralysis and paresis	15
Sputum, excessive	15
Dyspnea	12
Chills	7
Sweating	6
Sore throat	6
Reflexes, hyperactive	5
Hemorrhagic sputum	4
Anorexia	2
Visual disorders	2
Speech disorders	2
Staggering gait	1
Dizziness	1
Incontinence	1
Erythema nodosum	1

primary pulmonary coccidioidomycosis. It has been fully established that the disseminated form of the disease rarely follows if erythema nodosum is present in the early stages; furthermore, a permanent immunity to subsequent *C. immitis* infection seems to be acquired. It is interesting to note, however, that in the only fatal case in this series in which erythema nodosum did occur the infection was disseminated. The skin manifestations were

not present at the time of autopsy, and the gross lesions were found only in the lungs and the meninges. Only microscopic lesions were found elsewhere, and these were restricted to the spleen. The pulmonary lesion was a solitary focus well advanced toward healing; the more important and immediately fatal process was in the meninges. The duration of the illness in this case was 467 days. Erythema nodosum developed very early, as it usually does. Obviously this case is exceptional, since the development of erythema nodosum did not protect this patient against further injury by *C. immitis*.

4. *Physical findings in this series:* In the physical examination of this group of cases, disseminated lesions were found in a great variety of locations. In each instance the lesions produced their own peculiar physical disturbances, and therefore it is neither practical nor useful to attempt a detailed analysis of these findings. Certain general data relating to the state of the individual as a whole are, however, worth mentioning and commenting upon, as follows:

a. Loss of weight was a striking feature, often amounting to as much as 20 or 30 pounds in the course of a few weeks.

b. Fever occurred in all cases at some time, the temperature usually ranging between 100° and 103° F., rarely higher.

c. The pulse rate was found to range around 100 or less, with 130 as the highest mark.

d. No striking increase in respiratory rate was noted in any of the cases, the usual rate being between 20 and 30 per minute.

e. Blood pressure was never significantly altered.

f. The physical findings in the lungs varied enormously from case to case. When present, they consisted of (1) rales, (2) mucopurulent sputum, sometimes blood-streaked, (3) evidences of consolidation of a patchy or sometimes lobar distribution, (4) evidences of pleural effusion, usually minimal but sometimes massive, (5) occasional evidences of cavity formation. In the absence of physical findings, the condition of the lungs was most

often revealed only by roentgenograms, which demonstrated one or more of the following features: (1) hilar and mediastinal lymph node enlargement (Figs. 2, 3, and 4), (2) prominent bronchial markings, (3) focal or lobular consolidation (Figs. 2, 3, and 4), (4) homogeneous diffuse lobar consolidation, (5) focal, miliary and nodular consolidation, (6) solitary areas of consolidation with evi-

small papular nodules 5 to 10 mm. in diameter, superficially situated, (2) ulcerated nodules, (3) multiple verrucous lesions, (4) pustular furuncular nodules, (5) ulcerations representing the opening of sinuses leading from the subcutaneous tissues or the more deeply situated structures (Fig. 32), (6) chronic indurated ulcers, (7) erythema nodosum, (8) large subcutaneous suppurative

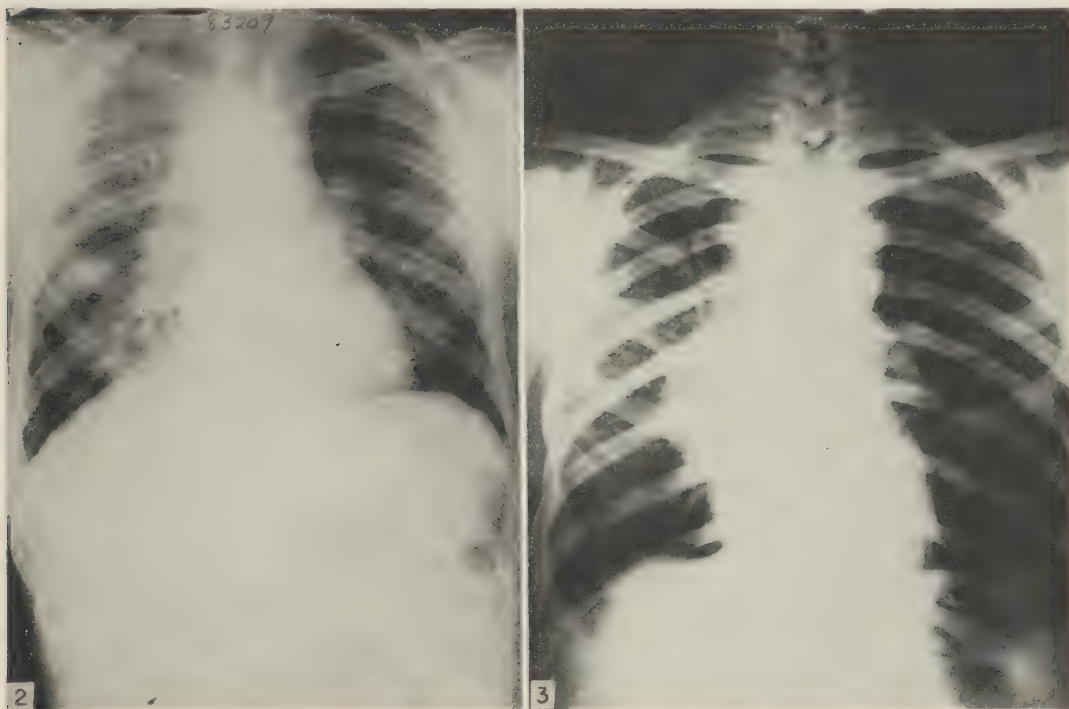


FIG. 2. Primary pulmonary coccidioidomycosis, AIP Ac. 83209: Roentgenogram of unilateral diffuse confluent bronchopneumonia with cavity formation, accompanied by massive mediastinal lymphadenitis. Death on 60th day of the disease with widespread dissemination of lesions. Gross appearance of the lung was not unlike that shown in Figs. 7 and 8.

FIG. 3. Primary pulmonary coccidioidomycosis, AIP Ac. 117769: Roentgenogram of unilateral lobular and confluent bronchopneumonia, somewhat wedge-shaped, accompanied by massive bronchial and mediastinal lymphadenitis. Death on 111th day of the disease, with meningitis and other disseminated lesions.

dence of encapsulation, (7) solitary areas of consolidation with centrally situated thin-walled cavities (Fig. 5); (8) multiple foci of calcification in the absence of any other change in the lung, (9) fibrous thickening of the pleura, (10) pleural effusion, either massive or minimal, (11) solitary dense tumor-like consolidation.

g. The lesions discovered in the skin and subcutaneous tissues were as follows: (1)

granulomatous masses or swellings, usually communicating with the surface of the skin by multiple sinuses and with the more deeply situated tissues, especially the bones, by complex infected and ramifying channels.

h. The bones clinically observed to be involved in these cases were as follows: rib, scapula, skull, clavicle, patella, vertebra, phalanges, tibia, sternum, ilium, sacrum, and ischium. As revealed by roentgenograms, the

bone lesions are sharply demarcated, but of a destructive character. They may be situated in the medullary canal, in the cortex or just beneath the periosteum; and they are not confined to any particular portion of the bones (Fig. 29). Complicated sinuses usually form communications between the lesions in the

cular symptoms are usually not referable to lesions within the muscles. However, muscular lesions were often observed, particularly in the psoas muscle, in which case they presented the same clinical manifestations as the psoas abscess of tuberculosis.

k. The usual physical signs of meningitis

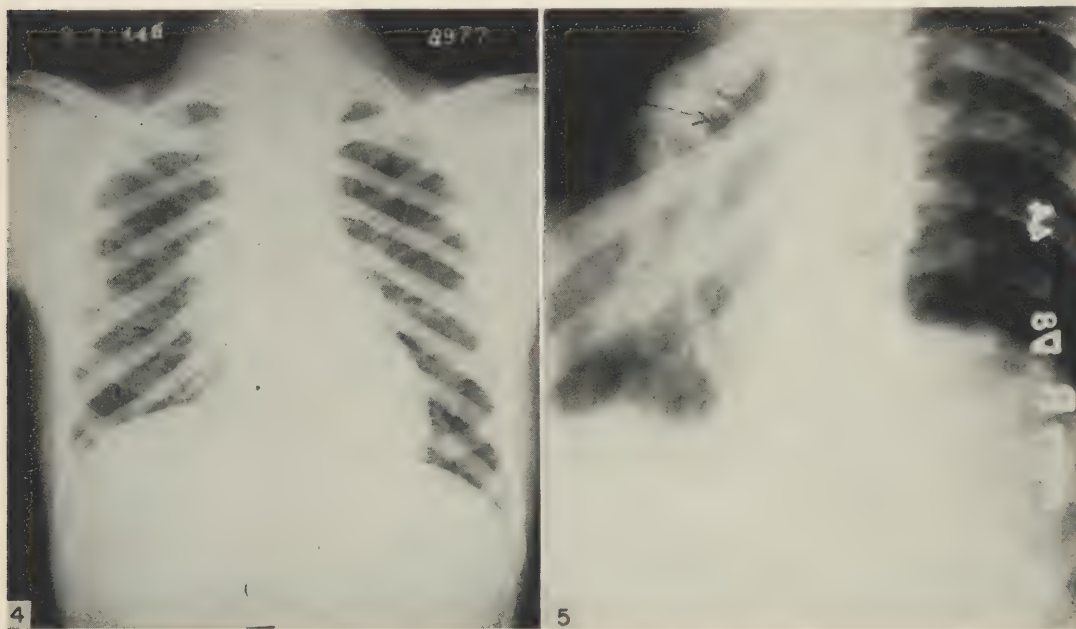


FIG. 4. Endogenous reinfection pulmonary coccidioidomycosis, AIP Ac. 150192: Roentgenogram of bilateral widespread diffuse and focal consolidation of the bronchopneumonia type, accompanied by bronchial and mediastinal lymphadenitis. Death on 274th day with widespread dissemination of lesions. Gross appearance of lung not unlike that shown in Figs. 6 and 7.

FIG. 5. Endogenous reinfection pulmonary coccidioidomycosis, AIP Ac. 150192: Roentgenogram of same lung as in Fig. 4, posed to show one of several cavities situated in the right upper lobe.

bone and the overlying soft tissues, finally discharging their contents through the skin (Fig. 30). In some instances the bone lesions are tumor-like in their general appearance, being readily mistaken for genuine neoplasms.

i. The joints were not frequently the site of the granulomatous process, but in some cases lesions were seen in the knee, the elbow, the ankle, the sterno-clavicular, the claviculo-acromial, and the sacro-iliac junctions. Involvement of the sterno-clavicular joint was noticeably frequent. The infected joints usually were found to communicate with adjacent bone lesions.

j. The rigidity, weakness, and other mus-

were demonstrated in a considerable proportion of the cases under discussion: diplopia, stiffness of the neck, positive Kernig's sign, and other indications of meningeal involvement.

l. Enlarged lymph nodes were found in 39 of the 95 cases, and usually were those draining infected areas. The mediastinal nodes were the most frequently involved, as indicated by both physical and roentgenologic examination of the chest. Sometimes the enlarged nodes were found to undergo suppuration, with the development of sinuses leading to the overlying skin.

m. Enlargement of the liver, suggesting

abscess formation, was observed in one case.

n. Typical signs of chronic peritonitis were observed in two instances, both of which proved to be peritoneal infection with *C. immitis*.

In Table VIII is shown the distribution of the more significant diagnostic physical findings in this series of cases.

TABLE VIII
DISTRIBUTION OF THE MORE SIGNIFICANT POSITIVE
DIAGNOSTIC PHYSICAL FINDINGS IN 95
CASES OF DISSEMINATED
COCCIDIOIDOMYCOSIS

	Total Number
Skin and subcutaneous tissues	64
Lung	51
Lymph nodes:	39
Cervical	23
Bronchial	29
Axillary	4
Inguinal	4
Retroperitoneal	3
Epitrochlear	3
Bone	29
Meninges	10
Joints	8
Peritoneum	3
Liver	1

5. *Blood findings:* A profound anemia has been found characteristic of this group of cases. It is usually associated with a moderate leukocytosis with a slight increase in the neutrophils and a marked eosinophilia. A composite picture of the blood findings is represented in Table IX. In the cases specified in Table IX, which were selected to suggest the range of the blood counts, the highest eosinophil count was found to be 34 per cent; the lowest red cell count, 2.2 million; the highest white cell count, 23,700; the highest lymphocyte count, 45 per cent; the lowest hemoglobin estimation, 50 per cent. In 53.8 per cent of the 26 cases tested the sedimentation rate was elevated.

The serologic findings in this group of cases are summarized in Table X.

Serologic studies were carried out in com-

TABLE IX
HEMATOLOGIC FINDINGS IN FATAL AND SURVIVING
CASES OF DISSEMINATED COCCIDIOIDOMYCOSIS

	Average
RBC in 38 cases (average of lowest counts)	3.5 million
Hemoglobin in 32 cases (average of highest counts)	64 percent
WBC in 45 cases (average of highest counts)	14,400
Neutrophils in 45 cases (average of highest counts)	73.5 percent
Eosinophils in 22 cases (average of highest counts)	8.6 percent
Monocytes in 10 cases	3.1 percent
Lymphocytes in 23 cases	21.9 percent
Sedimentation rate in 26 cases, elevated	53.8 percent

paratively few cases in this series. In only 6 were the studies complete, and although there are too few upon which to base any conclusions the results are of some interest. A strict parallelism was found between the results of the coccidioidin, precipitin, and complement-fixation tests in 4 of the cases. Parallelism between the precipitin and complement-fixation reactions also existed in 4. Parallelism between the results of the coccidioidin test and complement-fixation reaction was present in 5 cases. In 5 cases the coccidioidin and precipitin reaction ran parallel. From the data it appears that there is no relation between the complement-fixation by coccidioidin and by the syphilitic antigen. The data from the 6 completely studied cases are presented in Table XI.

Tuberculin reactions were tested in only 5

TABLE X
SEROLOGIC AND SKIN TEST FINDINGS IN FATAL AND
SURVIVING CASES OF DISSEMINATED
COCCIDIOIDOMYCOSIS

	Posi- tive	Nega- tive
In 28 cases, coccidioidin	16	12
In 22 cases, complement-fixation	20	2
In 13 cases, precipitin reaction	6	7
In 22 cases, Wassermann and/or Kahn reaction	4	18

of the 95 cases in this series, and 4 proved to be negative. These limited data do not support the view held by some of the earlier workers that a close correlation exists between the coccidioidin and tuberculin reactions in cases of coccidioidomycosis.

6. *Sputum findings:* The quantity of sputum produced by patients with disseminated

Organisms were seen in the exudate of 14 of 17 lesions examined. They were cultured from the exudate of 11 of 16 ulcerative lesions. Organisms were both seen and cultured in 5 cases; seen, but not recovered in culture, in 1 case; cultured, but not seen in the exudate, in 1 case. From these data it is obvious that the microscopic examination of exudates for

TABLE XI
SEROLOGIC AND SKIN TEST FINDINGS IN SIX CASES OF
DISSEMINATED COCCIDIOIDOMYCOSIS

	Coccidioidin	Precipitin	Complement-Fixation	Wassermann-Kahn
Case No. 4, AIP Ac. 95409	Negative	Negative	Positive	o
Case No. 8, AIP Ac. 108221	Positive	o	Positive	—
Case No. 37, AIP Ac. 117401	Positive	Positive	Positive	Positive
Case No. 45, AIP Ac. 108114	Positive	Positive	Positive	—
Case No. 53, AIP Ac. 117769	Negative	Negative	Negative	—
Case No. 79, AIP Ac. 130093	Positive	Positive	Positive	o

coccidioidomycosis, of which extensive pulmonary involvement is usually a characteristic feature, is surprisingly not large. Blood often appears in the sputum either as simple blood streaking or in considerable quantity. In a few instances actual hemorrhage from the lung occurred. Bloody sputum was observed in the absence of cavities in the lung. In only 3 of the 95 cases was the sputum purulent.

Study of the sputum for the presence of *C. immitis* was a common clinical procedure, but the results are not reliable because of difficulty in recognizing the organisms, especially the smaller forms. Sputum examination by microscopic preparations was made only in the 50 fatal cases. Eleven of these were found positive, representing an effectiveness of this method of diagnosis of 22 per cent. Obviously, this justifies the use of the procedure routinely. Sputum cultures revealed the organisms in 6 cases, and in 3 of these the organisms were seen in the sputum and subsequently cultured and identified.

These data on the finding of organisms in the sputum of fatal cases may be compared with data relating to the demonstration of organisms in exudate from ulcerative lesions.

the organisms is a useful diagnostic procedure, though not to be relied upon exclusively. In some of our cases animal inoculations have been made, the animals being guinea pigs, white rats, and white mice, all of which are highly susceptible to the infection.

7. *Spinal fluid findings:* In this series of 95 cases there were 8 cases of coccidioidomycotic meningitis. Examination of the spinal fluid from this group of cases revealed the findings listed in Table XII.

Organisms were seen in microscopic

TABLE XII
SPINAL FLUID FINDINGS IN CASES OF
COCCIDIOIDOMYCOTIC MENINGITIS

	Average
Total cell count, 14 cases	114
Lymphocyte count, 11 cases	59 percent
PMN cell count, 11 cases	41 percent
Globulin, 11 cases	Elevated
Pressure in 8 cases	Elevated (max. 600 mm. water)
Sugar in 6 cases	Elevated (max. 52 mg. %)
Color of spinal fluid	Usually cloudy or rusty



FIGURE 6. Endogenous reinfection pulmonary coccidioidomycosis, AIP Acc. 133706: Kodachrome photograph of the lung to show widespread granulomatous bronchitis and bronchopneumonia, the latter often confluent. Roentgenologic appearance like that in Fig. 4, except for greater density of the consolidation. See Fig. 19 for microscopic appearance of the lesion. Note the relative absence of involvement of the bronchial nodes. Death on 365th day with rapid pulmonary bronchial spread and widespread extrapulmonary dissemination.

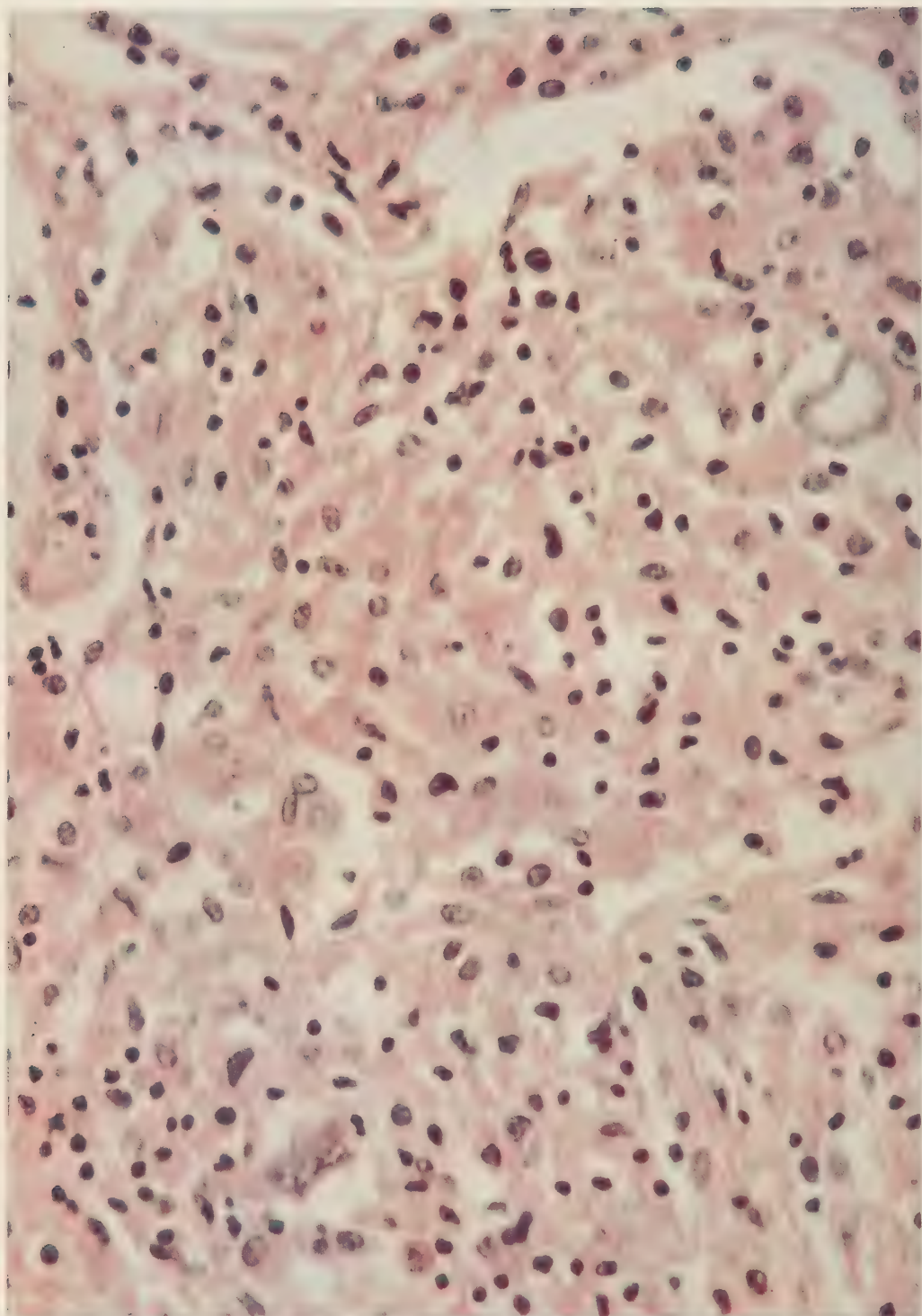


FIGURE 18. Primary pulmonary coccidioidomycosis, AIP Acc. 96443: Pure granulomatous lobular pneumonia. Note that the alveoli are filled with solid granulomatous tissue, while the alveolar walls remain intact. In the inflammatory tissue are seen two organisms, one in spherule form, the other maturing toward endosporulation. Death in 123 days.

preparations of spinal fluid in two cases, cultured from the spinal fluid in one case, and both seen and cultured in one case.

V

PATHOLOGIC ANATOMY OF COCCIDIOIDOMYCOSIS

The distribution of the significant diagnostic physical findings in the 95 cases (Table IV and VIII) indicates clearly the importance of certain organs and anatomic regions in the pathogenesis of coccidioidomycosis. Of the internal structures, the lungs, the lymph nodes, the bones, and the meninges are commonly involved; however, in clinical studies of coccidioidomycosis the skin and subcutaneous tissues have been found to be most frequently the site of granulomatous lesions. Post-mortem studies reveal a somewhat different order of frequency of involvement of the various tissues, as will be seen in Table XIII.

According to the observations recorded in this table, the order of frequency of involvement in disseminated coccidioidomycosis is as follows: lungs, lymph nodes, spleen, skin and subcutaneous tissues, liver, kidney, bones, meninges, adrenal, myocardium, brain, pericardium, and pancreas. The remaining tissues are involved only incidentally. In the following section will be discussed the lesions as found in the individual organs, particularly in the lungs, since the pathogenesis of this disease is concerned primarily with the development of the pulmonary lesion.

It has been the custom among those most familiar with clinical coccidioidomycosis to recognize three fairly distinct stages of development. Lee and Nixon²²³ list these as 1) the primary, 2) the intermediate or pulmonary, and 3) the progressive or disseminated. According to most workers, what Lee and Nixon refer to as the "primary stage" of coccidioidomycosis is not characterized by any pathologic-anatomic changes in the lung or elsewhere; it is, indeed, actually asymptomatic. The fact that the patient has the disease or has come in contact with the etiologic agent is indicated simply by a changeover from

a negative to a positive coccidioidin skin test. However, according to Lee and Nixon, a considerable proportion of persons infected with *C. immitis* for the first time do exhibit clinical signs and symptoms, and these are almost regularly referable to the respiratory system. Although definite anatomic alterations of the lung occur in this form of the disease, Lee and Nixon include this in their "primary" stage, rather than in their "intermediate or pulmonary" stage, even though they realize that in many, if not all of these cases progressive changes take place in the lungs which finally produce their "intermediate or pulmonary" stage of the disease. Indeed, the continuous progress of some cases results in the widely "disseminated" stage of coccidioidomycosis, usually referred to in the older literature as coccidioidal granuloma. (Fig. 6)

The non-symptomatic phase of the "primary stage" of coccidioidomycosis has never been studied at autopsy; therefore we have no reliable information on the anatomic state of the body related to this phase of *C. immitis* infection. Something is known of the anatomic state of the body in the symptomatic phase of the "primary stage" of coccidioidomycosis characterized by chest pain, cough, nasopharyngitis, and general malaise. This information has been gained very largely, though not exclusively, from roentgenologic studies, especially those of Carter⁸² and Colburn.²²⁰ The contribution of Colburn is based upon a careful study with follow-ups of an epidemic of 75 cases; a detailed clinical report of this epidemic will be found in the paper by Goldstein and Louie.²¹³ (See also the report of an epidemic of coccidioidomycosis occurring in 14 students by Davis, Smith, and Smith,¹⁹³ 1942). From these and other clinical studies of "primary" coccidioidomycosis of the symptomatic type, it is clear that this phase of the infection is accompanied by one or more of the following anatomic changes within the lung and adjacent structures:

- a. Hilar and mediastinal lymph node enlargement
- b. Bronchial inflammatory changes

TABLE XIII
DISTRIBUTION OF LESIONS IN 50 AUTOPSIES, BASED ON GROSS AND
MICROSCOPIC STUDY OF THE TISSUES

	Gross	Microscopic	Final
Lungs	43	43	43
Lymph nodes:			
Bronchial and mediastinal	32	30	36
Abdominal	16		
Retroperitoneal	12		
Cervical	7		
Spleen	29	35	35
Skin and subcutaneous tissue	32	9	32
Kidney	30	30	30
Liver	17	30	30
Pleura	25	5	25
Bones:			
Rib	17	20	24
Vertebra	14		
Skull	10		
Sternum	7		
Clavicle	6		
Ilium	6		
Hand	4		
Tibia	4		
Scapula	3		
Fibula	1		
Meninges (lepto)	18	18	18
Adrenal	13	16	16
Myocardium	5	14	14
Brain	7	12	12
Bronchi	3	10	10
Dura	8	7	8
Pancreas	1	8	8
Pericardium	7	7	7
Retroperitoneal tissues	5	—	5
Voluntary muscles	5	—	5
Peritoneum	4	3	4
Thyroid	—	4	4
Esophagus	3	3	3
Joints (sterno-clavicular 2, hand 1)	3	1	3
Prostate	—	3	3
Stomach	1	3	3
Bone marrow	—	2	2
Optic nerve	2	2	2
Pituitary	—	2	2
Trachea and larynx	1	1	1
Nasopharynx	1	—	1
Diaphragm	—	1	1
Spinal cord	—	1	1

- c. Focal or lobular consolidation of the pulmonary parenchyma, sometimes of a distinctly miliary nodular type
- d. Homogeneous, diffuse lobar consolidation
- e. Solitary areas of consolidation sharply defined, some with central cavity formation
- f. Pleural effusion, usually small but sometimes massive

g. Multiple, more or less isolated areas of consolidation with intervening disseminated focal miliary lesions

The pulmonary changes found have been observed to run their course and to clear up completely within a period of 3 or 4 months. Indeed, in the epidemic of 75 cases mentioned above, all of the patients were eventually re-

2) the generalized or disseminated form. The initial pulmonary disease may occur in symptomatic and asymptomatic stages. Indeed, there is much to be gained by adopting a classification of the pulmonary form of coccidioidomycosis analogous to that in tuberculosis, in which we recognize simply a primary complex (symptomatic and asymptomatic) and a re-



FIG. 7. Primary pulmonary coccidioidomycosis, AIP Ac. 108095: Duration of disease 120 days. Death after widespread dissemination of lesions. The lung lesions are: a) focal granulomatous bronchopneumonia, b) necrotizing bronchitis and confluent suppurative and granulomatous pneumonia with early cavity formation. See details in Fig. 8. Note the minimal involvement of the bronchial nodes.

turned to duty, although dissemination to distal portions of the body did occur in one case.

The asymptomatic form of "primary" coccidioidomycosis is recognized solely by skin test with coccidioidin, and it is impossible to differentiate clinically between the symptomatic phase of "primary" coccidioidomycosis and the "intermediate or pulmonary" stage of the disease. Thus, it would seem more logical to think of coccidioidomycosis as occurring simply in two forms, 1) the pulmonary form, and

infection. Adoption of this view appears to fit well the pathologic-anatomic observations made in the 50 autopsies under consideration. Our anatomic observations accordingly will be presented under the headings: A. Pulmonary coccidioidomycosis—1. The primary complex, and 2. Reinfection pulmonary coccidioidomycosis; and B. Disseminated coccidioidomycosis.

A. Pulmonary Coccidioidomycosis

1. *Primary Pulmonary Coccidioidomycosis*—*The Primary Complex*. For reasons given

above, only the end stages and the healing phases of the primary pulmonary complex have been available for anatomic and histologic study. Despite this handicap it has been possible to construct in a fairly satisfactory manner the pathologic-anatomic picture that develops in the course of the primary pulmonary infection. This has been accomplished by selecting fatal cases of less than 100 days duration, and supplementing data from these by the study of

total duration of the disease was 74 days (Figs. 12, 13, and 14). This lesion corresponds to the focal, fuzzy consolidation of the lung so commonly seen in roentgenograms during the early stage of the disease. An accentuation of the bronchial markings of the lung is also apparent, as well as considerable enlargement of the bronchial and mediastinal lymph nodes. The histologic picture of this pneumonia is not at all remarkable except



FIG. 8. Primary pulmonary coccidioidomycosis, AIP Ac. 108095: Necrotizing confluent granulomatous pneumonia, with cavity formation. Note the multilocular cavity at the center of the pneumonic area and the adjacent cavities from which the necrotic sequestrum has not yet been removed. The bronchial lymph node at the upper right corner shows minimal involvement, and the adjacent secondary bronchi are normal. Same lung as shown in Fig. 7, but different section.

primary pulmonary lesions excised surgically and roentgenologic material from clinical cases.

The primary lesions, some of which progress and some of which recede to disappear eventually, fall within the following categories:

a. Lobular focal pulmonary consolidation strongly resembling the ordinary type of bacterial pneumonia. This we have seen in our Case No. 7 (AIP Ac. 74661), in which the

for the organisms within the pulmonary exudate, which consists largely of polymorphonuclear leukocytes with a scattering of large mononuclear wandering cells, and a considerable amount of fluid without much fibrin. The lesions relate particularly to the terminal portions of the bronchial system and the immediately adjacent atrial and alveolar spaces. Other lesions in the same case exhibit beginning granulomatous transformation. Thus,

different stages of development of the lesion may be found in one lung. Almost everywhere the changes are intra-alveolar, and the character of the exudate is such as to make possible complete resolution without residual structural changes. Quite naturally, some lesions progress too far for complete resolution; these heal by the formation of microscopic scars, leaving the lung otherwise unaffected.

b. Extensive gelatinous focal or confluent lobular consolidation. We have observed this lesion in our Case No. 79 (AIP Ac. 130093), with a total duration of 87 days (Figs. 7 and 8). Its striking feature proved to be its wetness and in some instances the hemorrhagic character of the exudate. Histologically the lesion is found to be of an almost suppurative character, the exudate consisting largely of polymorphonuclear leukocytes, but with a considerably greater number of mononuclear wandering cells than found in the ordinary pneumonic type of consolidation. The lesion is patchy in distribution. Between the more solid areas of pneumonia there is a profuse exudation of fluid without much fibrin, in which large mononuclear cells, polymorphonuclear leukocytes, and a few lymphocytes are scattered. The outpouring of fluid and cellular exudate is almost exclusively intra-alveolar and is associated with the presence of the specific organisms in great number and unusual forms. The most impressive feature of this form of the reaction is the extensive necrosis. It involves both the exudate and the adjacent pulmonary structures and is of such a character that complete restitution of the normal lung architecture would be impossible upon healing of the lesion. In both its gross and microscopic features this lesion bears a striking resemblance to the gelatinous pneumonia of pulmonary tuberculosis with early caseation.

c. Necrotizing ulcerative bronchitis and bronchiolitis with bronchiectasis and bronchiectatic cavity formation. This lesion is illustrated in our Case No. 24 (AIP Ac. 107640), the total duration of which was only 31 days (Fig. 10). The infectious process in this case was highly destructive, resulting in the forma-

tion of cavities like those occasionally seen in roentgenologic examination of the living patient early in the course of the disease. These lesions may persist as chronic abscess-like cavities in the lung long after the primary pulmonary infection has run its course and the patient has recovered from the acute illness. Histologically the ulcerative bronchitis has a distinctly granulomatous character, but the reaction is noteworthy for the large number of organisms and the continued presence of masses of polymorphonuclear leukocytes. The bronchi are usually filled with exudate consisting largely of leukocytes, fibrin, and mononuclear wandering cells (Figs. 16 and 17).

d. Focal lobular, or massive lobar indurated, gray, moist but not wet, granulomatous consolidation. This lesion in brilliant form was observed in an individual who died after 75 days illness, our Case No. 27 (AIP Ac. 85443) (Fig. 9). The histologic appearance of this lesion stands in sharp contrast to that of the other three types just noted. The reaction is essentially granulomatous, whether the lesion involves only foci or large areas of the lung, even to the extent of lobar consolidation. The exudate is composed almost exclusively of mononuclear cells, many of which have been transformed into epithelioid cells or large multinucleated giant cells. Masses of exudate of this type fill the alveolar spaces but, strangely enough, do not tend to cross the alveolar boundaries, leaving these structures well preserved. There is much fibrin with this granulomatous exudate and some, although not conspicuous, fluid. Here and there are microscopic areas of suppuration in which the exudate consists exclusively of polymorphonuclear leukocytes. These little abscess-like lesions are sometimes hardly more than the size of an alveolus, but they may occupy a whole lobule. The distinguishing feature of this lesion is its solid character, its absence of necrosis, and the seemingly organized arrangement of the cells comprising the inflammatory exudate. In lesions of this type organisms are always conspicuous except in the areas of suppuration and are usually in the intermediate stages of ma-

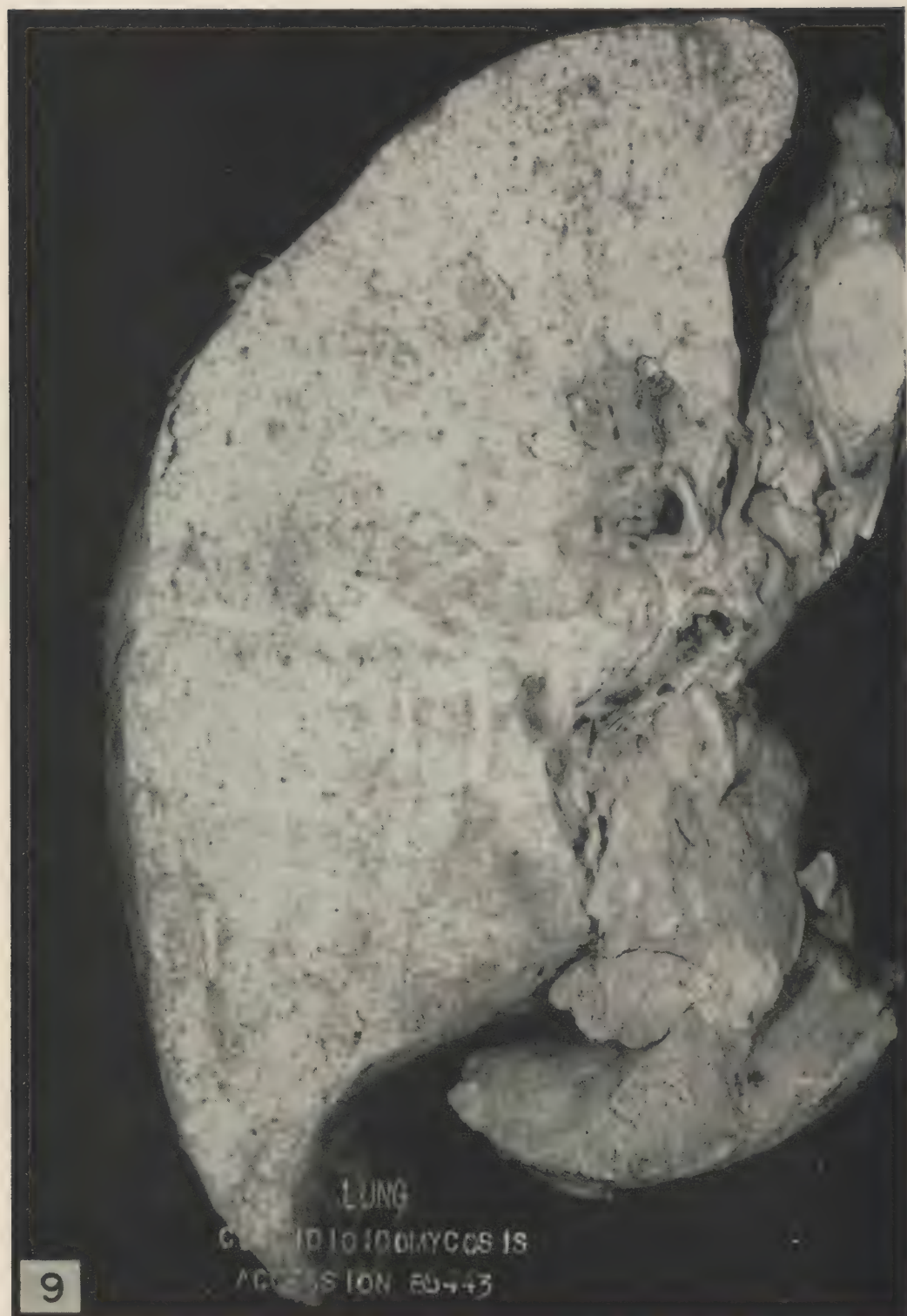


FIG. 9. Primary pulmonary coccidioidomycosis, AIP. Ac. 85443: Confluent lobular granulomatous pneumonia without conspicuous necrosis and little softening of the tissue. Caked consistency, firm and rubber-like, without fluid exudate; great enlargement and granulomatous alteration of the bronchial nodes with coagulative necrosis. Death on 75th day with extensive dissemination including meningitis.



FIG. 10. Primary pulmonary coccidioidomycosis, AIP Ac. 107640: Lung from a case with rapid course, death on 31st day of disease. Multiple focal suppurative lesions often in clusters where they become confluent and produce soft suppurating nodules. The lesions grossly and microscopically are distinctly suppurative and necrotizing like those shown in Figs. 16 and 17. Widely distributed extrapulmonary lesions.



FIG. 11. Chronic primary pulmonary coccidioidomycosis, AIP Ac. 156611: Lung with huge apical cavity with fibrous walls lined by necrotizing granulation tissue, removed by lobectomy. *C. immitis* cultured from pus in cavity. Unidentifiable hyphae and spores demonstrated in cavity exudate in sections. No spherules found in the tissues or in the exudate. Duration of pulmonary disease 9 years. This is the only case on record in which the mycelial form of the organisms have been found in tissues.

turation. They appear both intra- and extracellularly, being most conspicuous in the large multinucleated giant cells. The ultimate fate of this lesion, should the patient survive, can be only the transformation of the inflammatory lesion into a mass of hyaline scar tissue or eventual necrosis with partial fibrosis and encapsulation. Complete resolution of the lesion with restoration of the lung tissue to its normal state cannot occur. A massive lesion of the type just described is illustrated in

hyaline scars hardly larger than an alveolus. These scars are at times ossified. Completely hyaline or hyalinizing tubercles, solitary hard hyaline nodules as large as 2 or 3 cm. in diameter, usually with necrotic but firm centers (Fig. 24), and solitary or multiple cavities lined by chronic granulomatous inflammatory tissue (Figs. 25 and 26) are other forms observed in our material, chiefly in biopsy specimens and usually from patients who appear to be almost well. These chronic

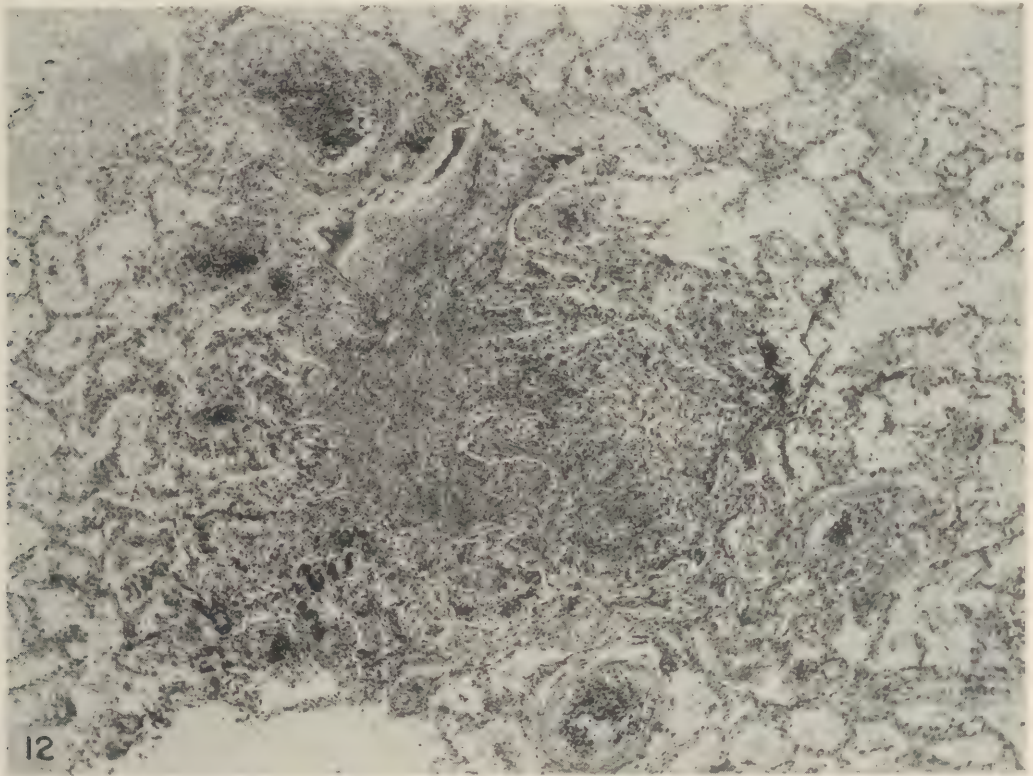


FIG. 12. Primary pulmonary coccidioidomycosis, AIP Ac. 74661: Microscopic appearance of earliest lesion encountered. Suppurative bronchitis with adjacent focal lobular pneumonia. Note bronchus filled with fibrinopurulent exudate; bronchial epithelium preserved in some small areas; adjacent alveoli filled with same exudate. Fibrin is not an outstanding feature. Death in 74 days. ($\times 60$)

Fig. 9. This form of pulmonary infection, like the others of the primary disease, is associated with hilar and mediastinal lymph node enlargement. The characteristic lesions in these lymph nodes resemble those in the lung.

e. Healed or progressively healing lesions. These lesions take various forms, although they are all essentially alike. Some of these consist of solitary or multiple minute focal

or healed lesions have been found in the cases of longest duration, ranging from 467 to 1,175 days (Fig. 11), and represent the healing of the primary foci. They are not thought to be related to the disseminated form of the disease.

So long as any one of these types of primary pulmonary complex exists, the danger of dissemination of the organisms into distal por-

tions of the body is always imminent. Active lesions of any one of the types mentioned may be progressive or regressive, which accounts for the variability of the clinical and roentgenologic picture in any given case. In some of the fatal cases of the disseminated form of coccidioidomycosis of relatively long duration a lack of consistent progressive clini-

cosis. The recurrence of extensive pulmonary disease after the original infection in the lung has been observed to recede or even to disappear constitutes what we have designated as reinfection pulmonary coccidioidomycosis. In case of complete resolution of the primary complex the source of the reinfection is from without the lung and adjacent tissues. When the

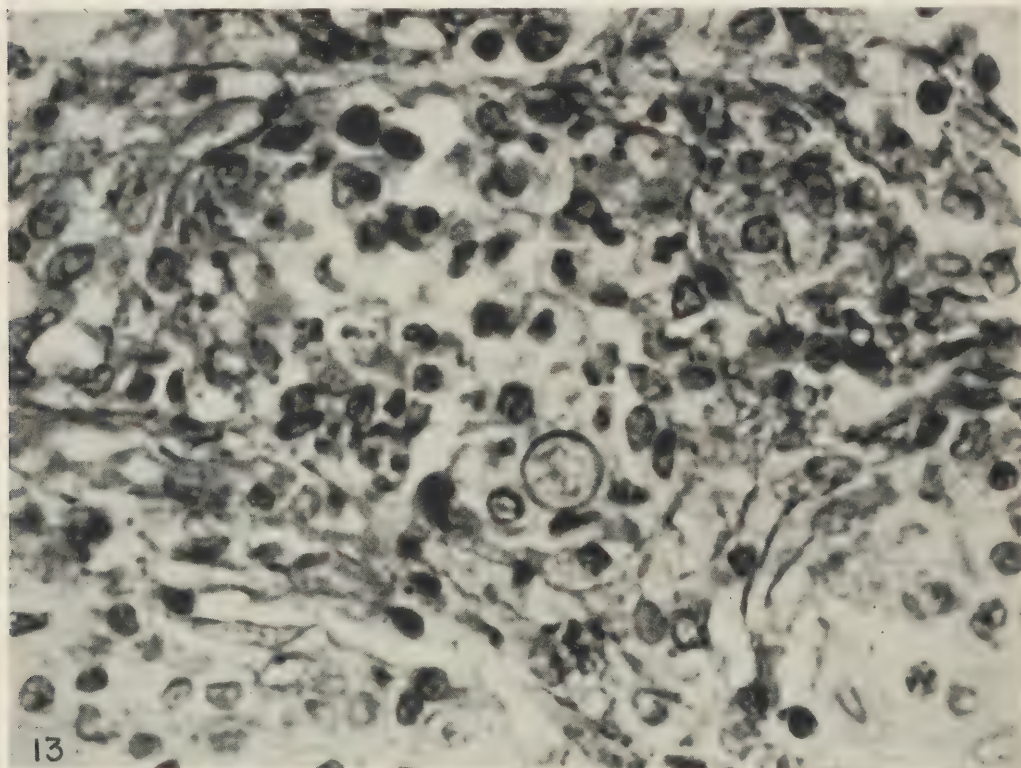


FIG. 13. Primary pulmonary coccidioidomycosis, AIP Ac. 74661: Under high power is seen a small section of lesion shown in Fig. 12, demonstrating the presence of organisms. Note the predominantly leukocytic character of exudate surrounding the organism. ($\times 1000$)

cal development of the pulmonary lesion may be the only means of differentiation between a primary pulmonary infection and a terminal reinfection of the lung. There may be such close anatomic resemblance between a progressing primary infection and a progressing reinfection of the lung acquired by late endogenous pulmonary dissemination, that the latter can be recognized positively only when pulmonary disease is known to have developed after the lung has been observed to clear completely from a preceding infection.

2. *Reinfection Pulmonary Coccidioidomy-*

primary infection has only receded, reinfection may occur from a destructive lesion in a bronchus, perhaps in association with adjacent necrotic infected lymph nodes. The result is then a fairly certain, wide, massive dissemination of infectious material into the lung tissue by way of the bronchial system. This bronchial spread theoretically might occur also after the disseminated form of the disease has developed, or indeed after all lesions except those of the bronchial and mediastinal lymph nodes have subsided. A somewhat similar bronchial spread takes place during the course

of the primary pulmonary infection merely through the aspiration of infected bronchial contents from one part of the lung to another. This is the most obvious explanation of the variable roentgenologic picture in the lung in the primary pulmonary disease. These bronchial forms of reinfection of the lung stand in sharp contrast to the reinfection from the

will be recognized that here the analogy to tuberculosis is close. A good example of reinfection of the lung from an extrapulmonary focus long after the original pulmonary lesion had healed is found in our Case No. 84 (AIP Ac. 133706), Figs. 6 and 19.

It was not easy to determine from the material at our disposal either the portal of entry

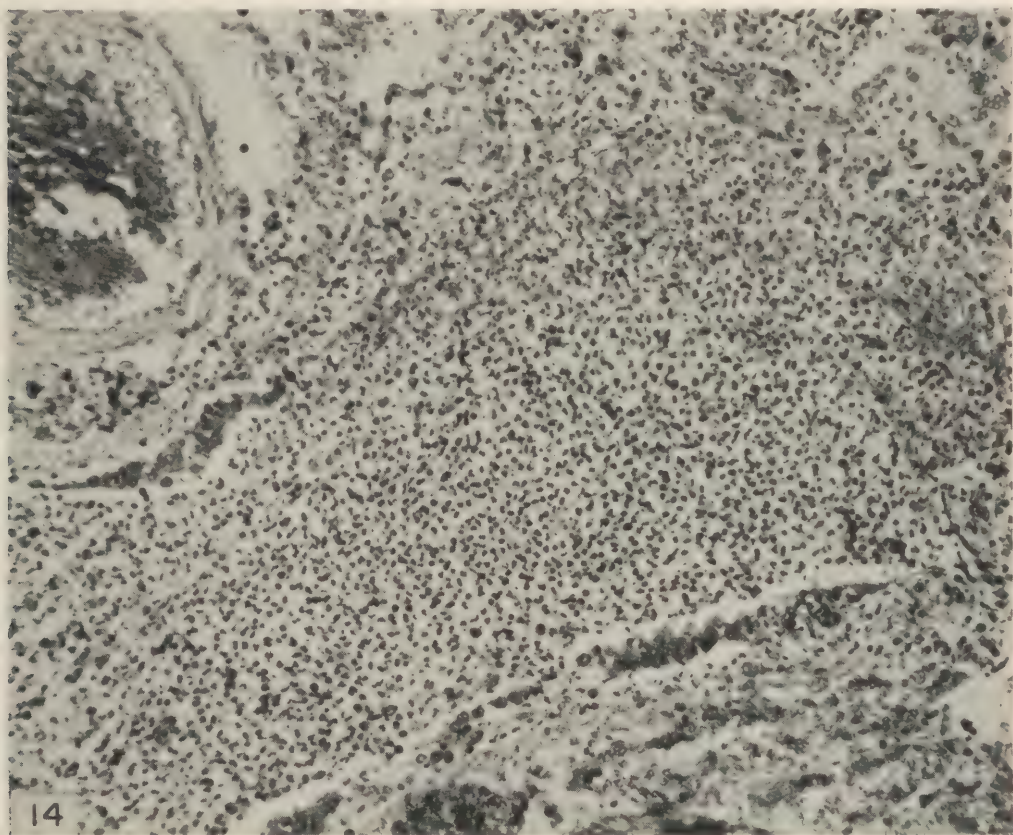


FIG. 14. Primary pulmonary coccidioidomycosis, AIP Ac. 74661: Higher magnification of bronchus in Fig. 12. The acute suppurative bronchitis accompanying the early stages of coccidioidomycosis. The exudate is made up of abundant polymorphonuclears, some fluid, fibrin, and cellular debris. The bronchial epithelium is preserved in a few small areas. ($\times 100$)

extrapulmonary disseminated lesions, when the organisms are brought to the lung by way of the blood stream to produce a widespread miliary type of infection. In pulmonary reinfection of this kind the bronchial and mediastinal lymph nodes do not react as in the primary pulmonary infection. They are often found to be relatively small in comparison with the large, succulent and often necrotic lymph nodes of the primary pulmonary complex. It

of the organisms into the blood stream or the foci of lodgement of the circulating organisms within the lung. The lesions in the lung have the appearance, both in the roentgenogram and in sections, of miliary nodules, like those in miliary tuberculosis; but close histologic study shows that the blood vessels are remarkably uninvolved by the infectious process. The lesions are often discrete, but may coalesce, in the latter case presenting a picture like that of

a spreading pneumonia with exudation, chiefly in the alveolar spaces. The lesion is indistinguishable from the focal lesions which follow aspiration of infected material (Fig. 6). These lesions most frequently develop about the bronchi to produce a gross picture not unlike that characteristic of the nodular type of interstitial pneumonia produced by bacteria, particularly the influenza bacillus.

monary terminal involvement produced by endogenous pulmonary spread and massive reinfection of the lung by way of the blood stream from extrapulmonary suppurative foci. (In two of our fatal cases there was no question of the origin of the massive pulmonary reinfection from a bronchial spread of the organism. Suppurative lymph nodes in the mediastinum had ulcerated through the wall

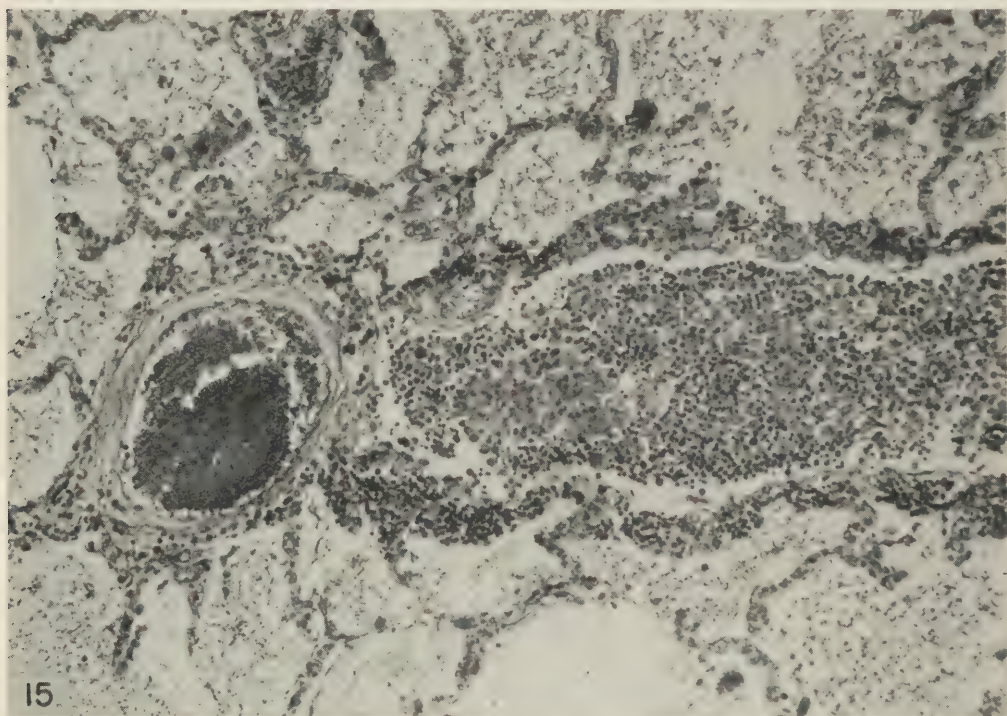


FIG. 15. Primary pulmonary coccidioidomycosis, AIP Ac. 74661: An area of Fig. 12, under higher magnification, demonstrating the lymphatic involvement as part of the primary lesion. The lymph vessel is crowded with monocytes, polymorphonuclears and fluid. The walls are involved in the inflammatory reaction, making it a real lymphangitis, which will lead to the bronchial and mediastinal lymph node involvement. ($\times 145$)

The great frequency of massive pulmonary disease in all fatal cases of coccidioidomycosis (in this series 43 of 50 cases), when viewed in the light of the known tendency of the primary pulmonary disease to heal, leaves little doubt of the development of an extensive hematogenous dissemination of the organisms to the lung in the terminal phases of the disease, particularly in protracted fatal cases. In those of short duration it may prove extremely difficult to distinguish between massive pul-

of the bronchus in one instance and the trachea in the other, and spilled their infected contents into the lumen of these structures. The material was then aspirated directly into the lung. These cases are No. 42, AIP Ac. 95411, and No. 73, AIP Ac. 114420.)

In practically all cases of coccidioidomycosis where the lungs are involved there is concurrent involvement of the pleura. This takes a variety of forms; the simplest is a fibrinous inflammatory reaction which gives rise to deli-

cate adhesions between the pleural surfaces. When the pleura is heavily infected, fibrino-purulent exudate is produced; and eventually a fairly thick granulomatous reaction occurs in which there may be a considerable amount of necrosis. The gross appearance of the pleura is then somewhat reminiscent of fibrocaseous pleurisy of tuberculosis. Abscess-like pockets

is impressively large. It was derived from an enumeration of all instances where pleural adhesions were found. It is common for the pleura to become secondarily involved when a disseminated lesion develops in the wall of the chest, particularly in the rib. Complicated sinuses may form communications between the pleura and the lesions in the chest wall. Active

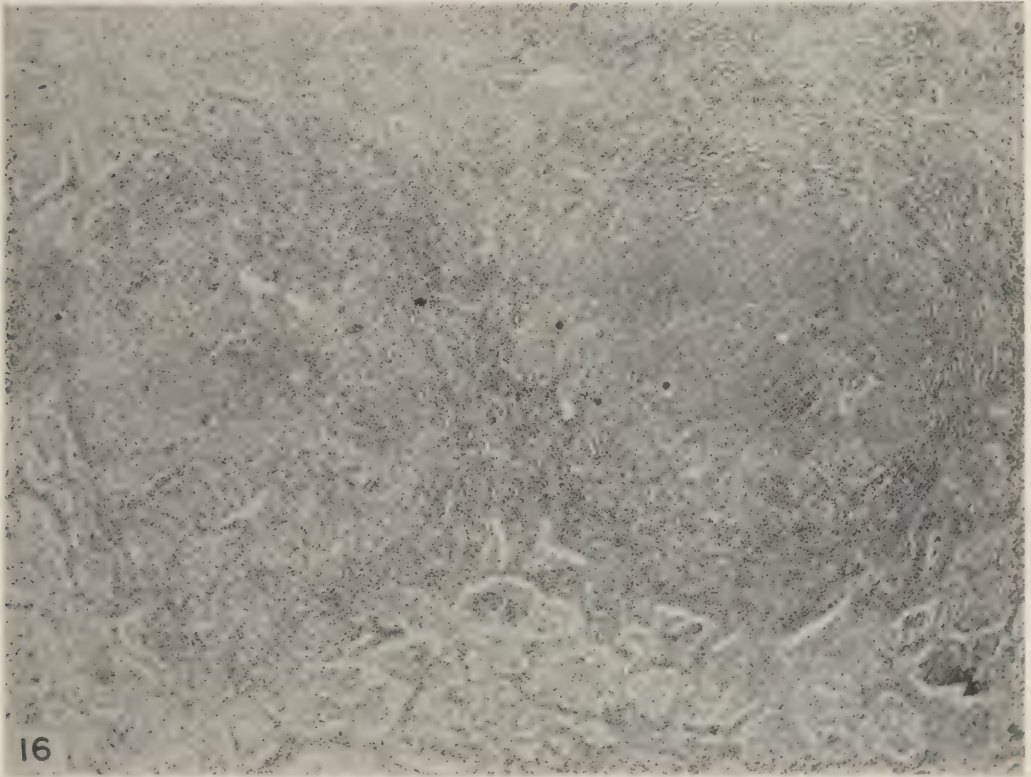


FIG. 16. Primary pulmonary coccidioidomycosis, AIP Ac. 114420: Focal suppurative necrotizing lobular pneumonia. In this lesion are found an abundance of organisms. The small abscesses seen will become the cavities of early pulmonary coccidioidomycosis. The corresponding gross picture is represented by the necrotic white nodules in the lung of Fig. 10. Death occurred in 94 days. ($\times 60$)

are sometimes observed in the earliest stages of infection of the lung. If these lesions reach the pleural surface, the infection gives rise to an immediate serofibrinous exudate, which may increase to the extent of 300 or 400 c.c. within a relatively short time. Ordinarily, however, the amount of fluid within the pleural cavity remains small, just enough to obliterate the angles above the diaphragm. In Table XIII the figure representing the gross involvement of the pleura in our autopsy cases

infectious processes were found in the pleura in only five of the series of 50 cases.

B. *Disseminated Coccidioidomycosis*

In the advanced and terminal stages of disseminated coccidioidomycosis specific lesions may be found in virtually any part of the body (Table XIII). The general characteristics of the lesions and the histologic reactions are quite the same regardless of the location; therefore only the more important secondary

lesions will be discussed, that is, those which are of sufficient importance to be considered somewhat in the nature of clinicopathologic entities.

1. *The Lymph Nodes.* The lymph nodes most commonly affected are the bronchial and

granulomatous fungus infections, particularly blastomycosis.

One of the reasons for the importance of involvement of the lymph nodes in this disease is that they often become necrotic, ulcerate, and discharge their contents into neighboring

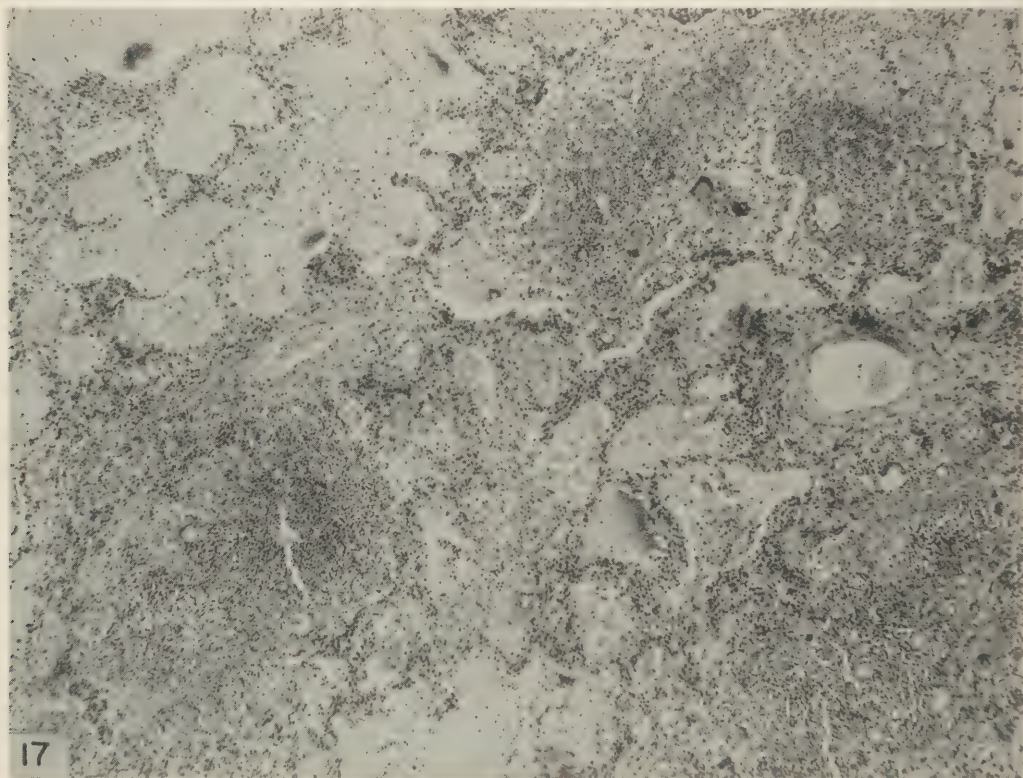


FIG. 17. Primary pulmonary coccidioidomycosis, AIP Ac. 74661: Early granulomatous lobular pneumonia. Besides the small abscesses there is already a focal granulomatous response in which some giant cells can be seen. Note the abundance of organisms in the abscesses. ($\times 60$)

mediastinal. These are always enlarged since they form a part of the primary infection complex in coccidioidomycosis. The lymph nodes become involved not simply by the passage of organisms from infected areas which they drain, but also through the lodgement of organisms by way of the blood stream in the lymphoid tissue. This accounts for the involvement of lymph nodes throughout the body in the long-standing and fatal cases. The frequent extension of the infection to the nodes very early in the disease was emphasized by Hektoen,⁹ who contrasted this feature of coccidioidal granuloma with that of other

tissues. The breakdown of lymph nodes with the formation of mediastinal abscesses, which in turn discharge their contents into the neighboring structures, for example, the esophagus and the trachea, occurred in two cases of this series. In one of these, extensive ramifying sinuses led from the mediastinal abscess up into the root of the neck, from which the accumulating pus was discharged through multiple sinuses in the skin. In another of our cases the epitrochlear lymph nodes became involved as a secondary effect in relation to a granulomatous suppurating lesion in the proximal phalanx of the little finger on the

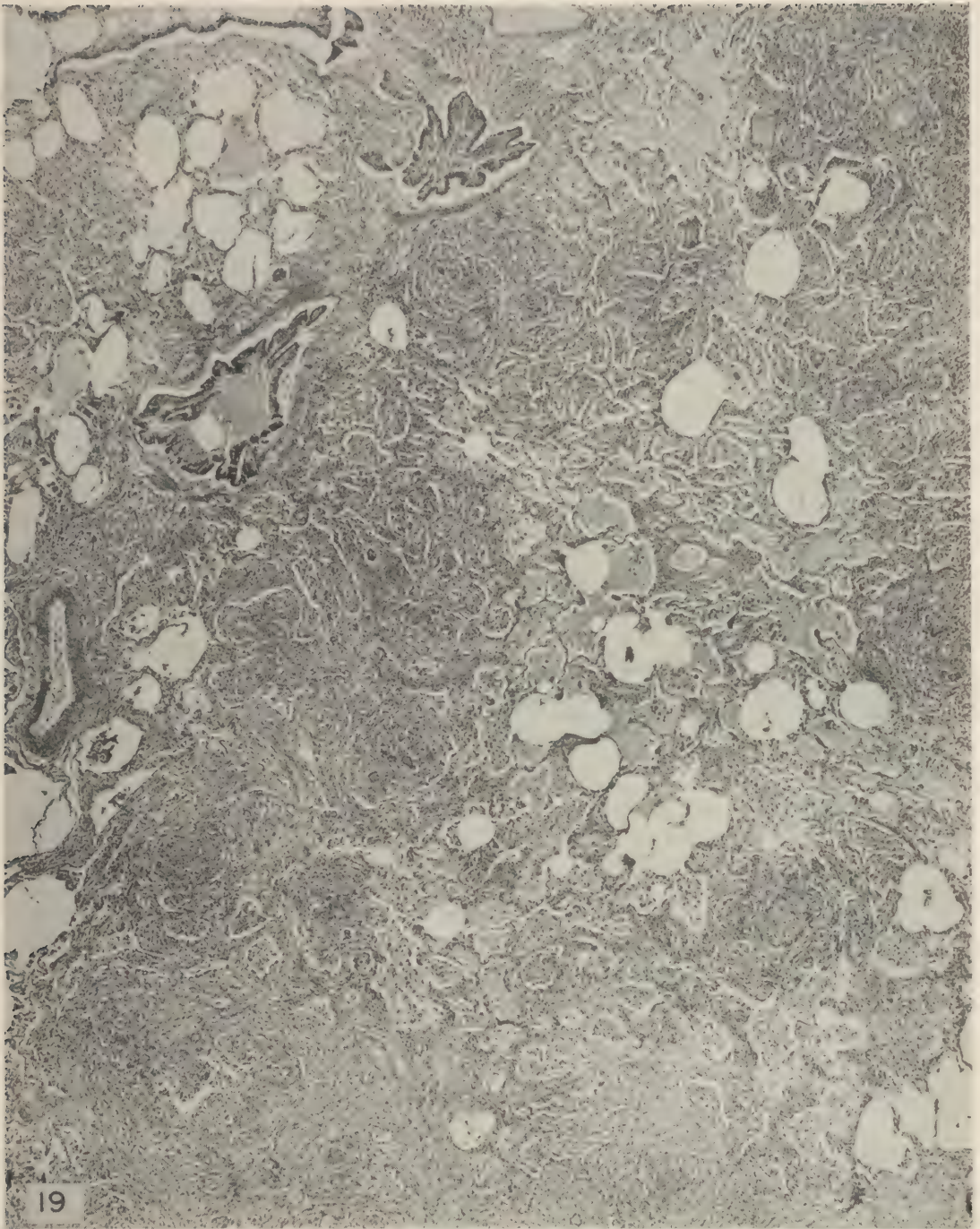


FIG. 19. Endogenous reinfection pulmonary coccidioidomycosis, AIP Ac. 133706: Microscopic appearance of lung in Fig. 6. Small abscesses are seen in some areas. In other areas is noted a typical granulomatous reaction filling the alveoli, whose alveolar walls are intact. Death in 365 days. ($\times 40$)

corresponding side. This case was our No. 81 (AIP Ac. 131556).

The enlargement of the lymph nodes is due to extensive granulomatous and suppurative necrotizing inflammatory lesions developing within them. These lesions tend to heal, just as

ation and death of the parasites. It is important to note that lymph nodes remain infected for a very long time and undoubtedly form a nidus for the propagation of organisms, and thus serve as a source for dissemination to other parts of the body.

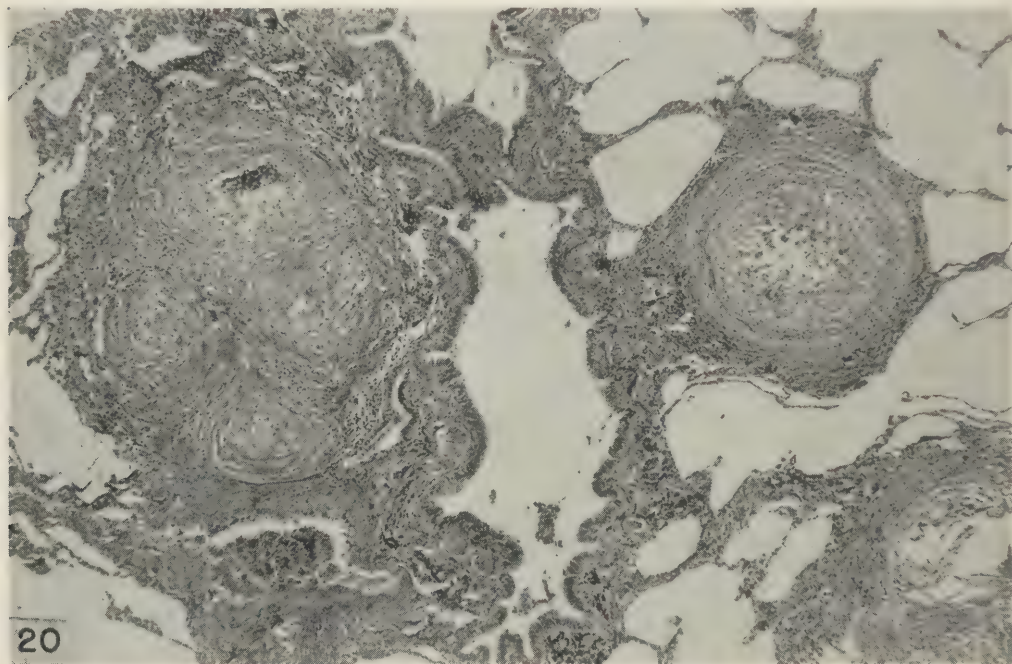


FIG. 20. Healing pulmonary coccidioidomycosis, AIP Ac. 159164: Adjacent to a bronchus are typical tubercles. A spherule can be seen in the tubercle, which is already well walled off by a fibrous capsule. Higher magnification of this tubercle is seen in Fig. 23. Death in 467 days. ($\times 65$)

do the lesions elsewhere in the body, and leave dense hyaline scars quite like those which follow the healing of tuberculous granulomatous lesions. In the freshly infected lymph nodes, where the organisms are particularly numerous, extensive necrosis occurs. Some of the nodes which we have examined in this series were hardly less than a massive culture of organisms embedded in highly necrotic tissue; others were extensively scarred with actual hyalinization of the scar tissue, in the presence of an extraordinary number of organisms. The organisms seem to persist and to proliferate. Some of the most indurated nodes, and some that appeared to be least active grossly, were found on microscopic examination still to harbor great numbers of organisms, as well as many forms resulting from degener-

2. *The Spleen.* Involvement of the spleen is exceeded in frequency only by that of the lymph nodes and is the result of both direct infection through the blood stream and the indirect effect of the infection, arising from general intoxication. Thus, there are specific coccidioidal granulomas, and, in addition, the acute splenic tumor which characterizes so many infectious diseases. As a result of this combination of lesions, the spleen is often considerably enlarged, its average weight in 27 cases being well over 200 Gm., with the largest weighing 700 Gm., the smallest only 78 Gm. This enlargement is chiefly the result of the acute splenic tumor. Although the specific lesions take a variety of forms, they ordinarily are not bulky (Fig. 29).

The most common lesions are focal miliary

nodules produced by the granulomatous inflammatory reaction. These are usually numerous, fairly soft, and suppurative changes occur within some of them. At times the larger necrotic nodules break down completely, forming chronic abscesses. Lesions of this sort may be solitary. A striking form of infection in the

throughout the splenic pulp. In more heavily infected individuals, these organisms can be found in great abundance, many of them being within the splenic sinuses and, thus, well on their way toward hematogenous dissemination. We have not seen any lesion comparable to the calcified nodules or hyaline foci so com-

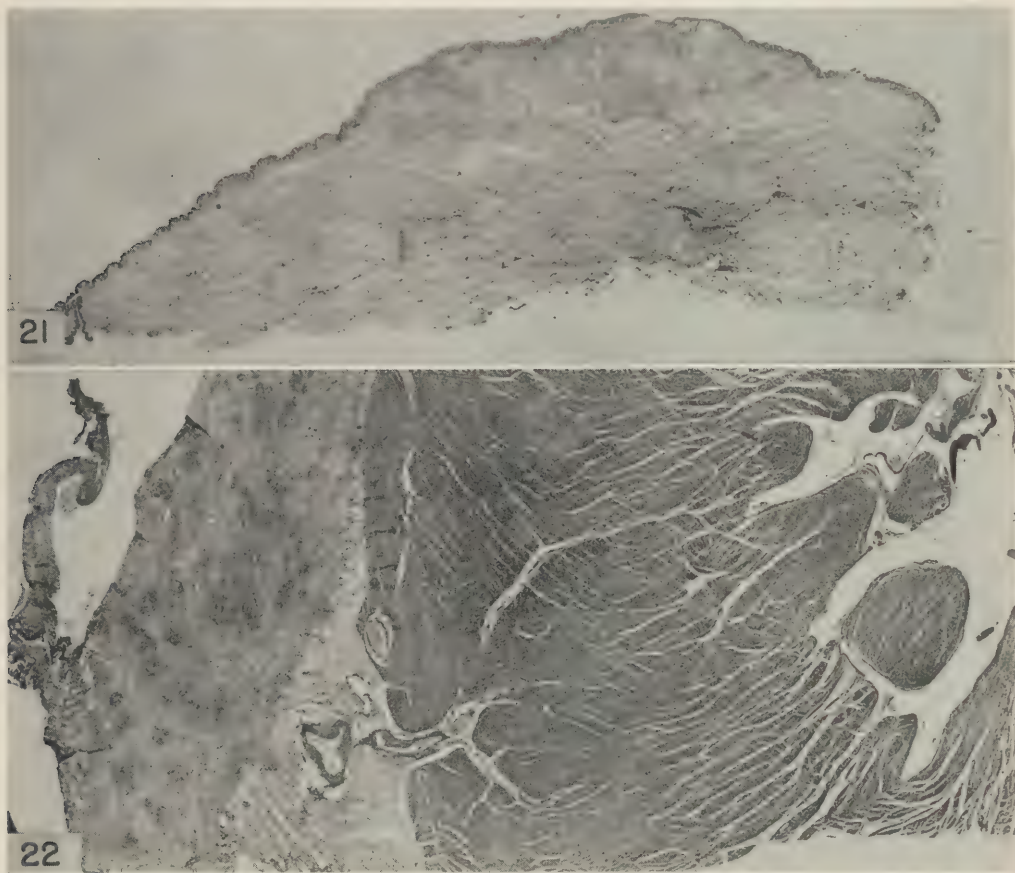


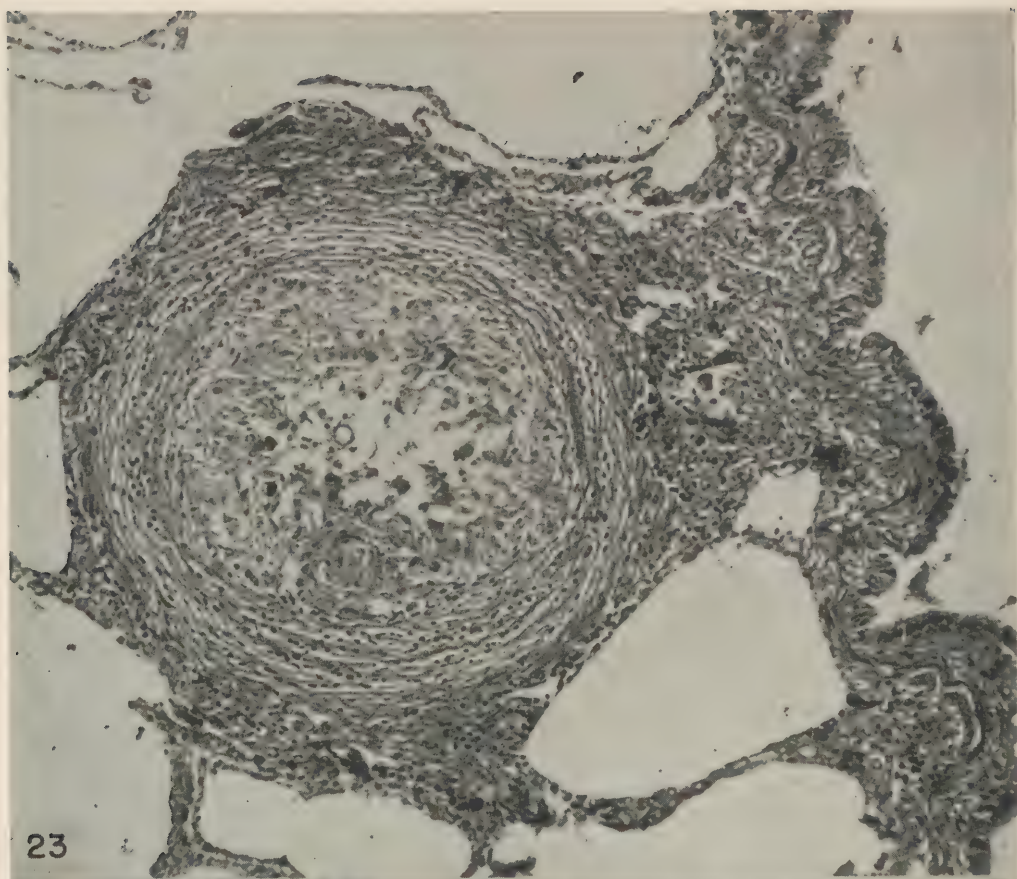
FIG. 21. Disseminated coccidioidomycosis, AIP Ac. 127046: This is a disseminated skin lesion under low power. Note the intact epithelium and subcutaneous necrosis. Death in 47 days.

FIG. 22. Disseminated coccidioidomycosis, AIP Ac. 96943: This demonstrates the granulomatous epicarditis. Note adhesion. From the epicardium the disease spread to the pericardium. ($\times 512$)

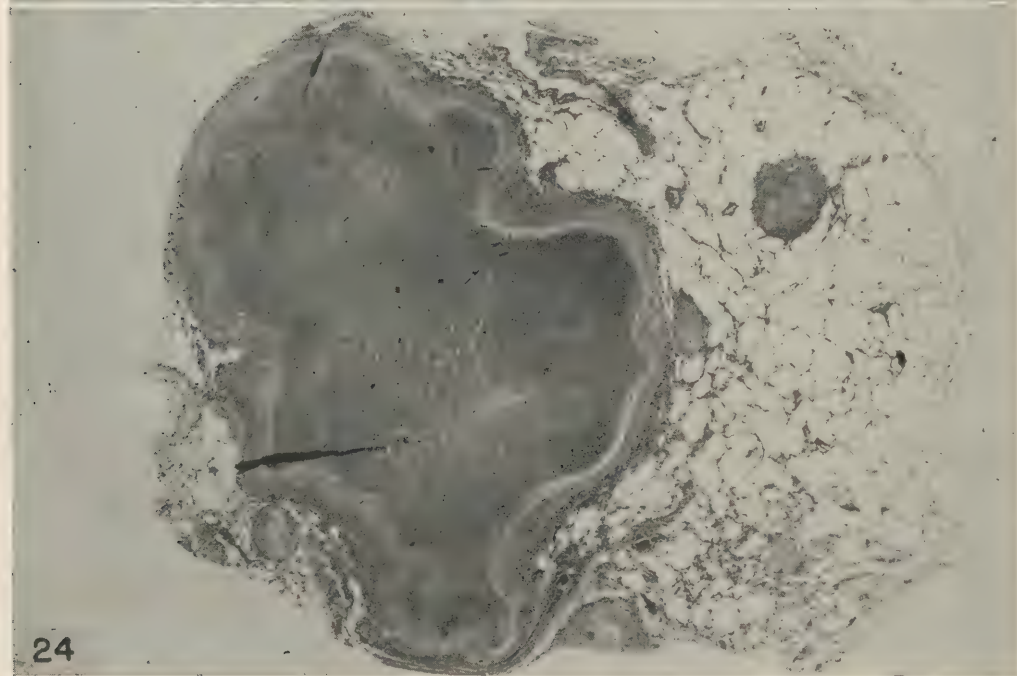
spleen consists of multiple minute abscesses. These little foci of suppuration appear by the thousands in the splenic substances and, interestingly enough, organisms are rarely visible within them. That organisms are present, however, can be demonstrated by the proper staining techniques, the ordinary Goodpasture-McCallum bacterial stain being satisfactory. Another highly interesting histologic detail is the widespread dissemination of organisms

mon in the spleen in disseminated tuberculosis, a disease to which disseminated coccidioidomycosis has so great but so superficial a resemblance.

3. *The Skin and Subcutaneous Tissues.* In this group of cases lesions in the skin and subcutaneous tissue were numerous (Table XIII). The cutaneous lesions are of two varieties: those related specifically to the infection with *C. immitis*, and those which relate



23



24

FIG. 23. Healing pulmonary coccidioidomycosis, AIP Ac. 159164: Higher magnification of the tubercle, which is well encapsulated, seen in Fig. 20. ($\times 60$)

FIG. 24. Healing pulmonary coccidioidomycosis, AIP Ac. 159164: This tubercle has progressed into the final stage of necrosis and is surrounded by a fibrous capsule. Eventually the whole lesion will be transformed into a dense scar. ($\times 60$)

to the degree of sensitization to products of these organisms. The most common lesion of the second type is erythema nodosum, and occasionally erythema multiforme. This we have seen in only one instance, and that occurred well in advance of the death of the patient, that is, in the earlier phases of the development of the pulmonary manifestations.

related directly to infection with *C. immitis* take a variety of forms, as listed on page 671. Histologically the lesions in the skin are quite like those elsewhere, the reactions being typically granulomatous with foci of suppuration (Fig. 21). They may occur anywhere over the body, but in our cases have been most frequent on the chest wall, the face,



FIG. 25. Healing pulmonary coccidioidomycosis, AIP Ac. 149019: This necrotic lesion shows a central cavity in which numerous organisms are still present. The surrounding lung tissue is collapsed. Note the patent ulcerated bronchus in the left lower corner. ($\times 5\frac{1}{2}$)

Few cases of primary pulmonary infection in which erythema nodosum occurs progress to the disseminated form. The absence, or virtual absence, of erythema nodosum and other manifestations of sensitization would seem to indicate that all of our cases have advanced well beyond the stage of primary pulmonary infection. This, of course, is in harmony with the actual findings. In this series we have had no opportunity to study the histologic reaction of the tissues showing the lesion in the skin.

Lesions in the skin and subcutaneous tissues

and the scalp. The frequency with which the skin overlying the sterno-clavicular junction has been involved is striking.

4. *The Liver and the Kidneys.* Within the abdominal cavity the lesions of disseminated coccidioidomycosis are more often found in the liver and the kidneys than in any other organ except the spleen. The changes in the liver are similar to those in the spleen, with enlargement resulting from the general intoxication in addition to the specific lesions of *C. immitis*. The specific lesions in the kidney are like those

occurring in the liver and consist of isolated granulomas in various stages of development. The lesions are usually quite small, of the miliary type, and are scattered through the parenchyma without localization in specific portions of the lobule. In both of these organs it is not unusual to find, along with the typical miliary granulomas, abscess-like suppurative lesions of about the same size. The lesion

all. Although the infection may occur in any portion of the bone and periosteum, it is perhaps most commonly seen at the ends of the bones, particularly in relation to the bony prominences, such as the tibial tubercle, the ankle, the acromial process of the scapula, and the medial extremity of the clavicle. When the infection develops in the cancellous bone of the epiphyses, it may destroy the overlying articular



FIG. 26. Healing pulmonary coccidioidomycosis, AIP Ac. 149019: A higher magnification of the bronchus surrounded by the necrotic infectious material, seen in Fig. 25. From such relatively old lesions organisms may disseminate, resulting in pictures as in Figs. 6 and 19. ($\times 25$)

usually seen in the liver and the kidney is illustrated in color photograph (Fig. 28). In one of our cases a portal phlebitis of granulomatous type developed. In no instance have we seen infection of the pelvis of the kidney or of the ureter.

5. *The Bones.* Coccidioidal granulomatous infection of the bones constitutes one of the most characteristic features of this disease. Usually a number of bones are affected, but the type of reaction is essentially the same in

cartilage, and thus involve the joint. Infection of the skull is not only one of the most common bone lesions, but one of the most important because of the extension of the process both inward and outward. The former gives rise to coccidioidal infection of the pachymeninges, which may eventually extend to the subarachnoid space, resulting in a usually fatal meningitis. Outward extension from the skull, as from other bones, results in the formation of large subcutaneous abscess-like lesions which

drain persistently, when once they rupture through the overlying skin.

One of the most interesting bone lesions occurs in the bodies of the vertebrae. Here the infection is in the cancellous portion originally, but it extends to become subperiosteal. If this occurs in the vertebrae of the lumbar region, the infection may extend through the attachments of the muscles, particularly through those of the psoas muscles, in which event it forms a typical psoas abscess resembling that which occurs in tuberculosis of the vertebral bone. In a relatively large proportion of delayed disseminations the first manifestation of the dissemination was found in a swelling of one of the bones, often of the small bones of the hand. Involvement of the ribs, like that of the vertebrae, is especially important because of the relation to adjacent structures, in this case the pleura and the overlying skin. Large abscess-like lesions within the thoracic wall were common in the cases we have studied. They usually erupt on the surface, but they may produce widespread dissection of the chest wall before discharging through the skin. The sternal lesions are prone to develop at the sterno-clavicular junction, but the reason for this is not apparent. Specimens of the gross lesions of the bone, except of the ribs, vertebrae, sternum, and skull, were not included in our material; but our roentgenograms have provided a clear picture of the lesions in these and the other bones when they were involved.

6. *The Adrenals.* *C. immitis* rather frequently localizes in the adrenal, to judge from our series, in which the gland was involved in 16 of the 50 cases studied at autopsy. In no instance was the adrenal tissue completely destroyed, but in a number both adrenals were infected. The lesion usually consists of one or more granulomatous nodules. No indication of adrenal insufficiency has appeared as a result of the granulomatous changes in this organ.

7. *The Heart and its Coverings.* In 14 instances the myocardium was found to be the seat of disseminated granulomatous lesions, most of them miliary, some microscopic, and not particularly numerous in either case. In some instances the lesions were situated in the

superficial portion of the muscles, involving the epicardium (Fig. 22). Pericarditis due to *C. immitis* infection in 7 of the 50 autopsied cases appeared to have resulted from the eruption of a superficially situated granulomatous lesion located in and just beneath the epicardium. This mechanism of infection of the serous membranes was observed elsewhere in the body, for example, in the peritoneal cavity and in the subarachnoid space. In none of the 14 cases in which the myocardium was involved was an endocardial lesion found. Focal granulomas sometimes were present just beneath the endocardium of the ventricles, but never in any of the valves of the heart. It appears that endocarditis of the usual bacterial variety does not occur in coccidioidal infection (for a possible exception to this, see Epstein¹⁴⁹), an observation which has also been made in tuberculosis and in other fungus infections, such as blastomycosis. Serofibrinous pericardial effusion resulting from infection of the pericardial surfaces and fibrous adhesive pericarditis with foci of necrosis simulating caseation were observed in the series.

8. *The Brain and the Meninges.* Dissemination of *C. immitis* to the brain results in sometimes solitary but usually multiple granulomatous lesions. These may take the form of miliary nodules which may be firm, soft, and necrotic, or definitely hemorrhagic. Solitary granulomas of considerable size (2 to 3 cm.) have been observed and are like those that develop in other tissues. It is important to note, however, that these lesions develop both superficially and deeply in the brain. Our observations indicate that infection of the brain substance is not nearly so common as in tuberculosis; therefore infection of the meninges could not often result from the process of extension. Since the organisms are of sufficient size to lodge readily within the vessels of the subarachnoid space, it is possible that the infection of the meninges may be brought about through this mechanical factor.

The meningitis that we have seen in disseminated coccidioidomycosis is of two essential varieties: 1) a firm, plastic type of meningeal inflammation, which results in the encasement

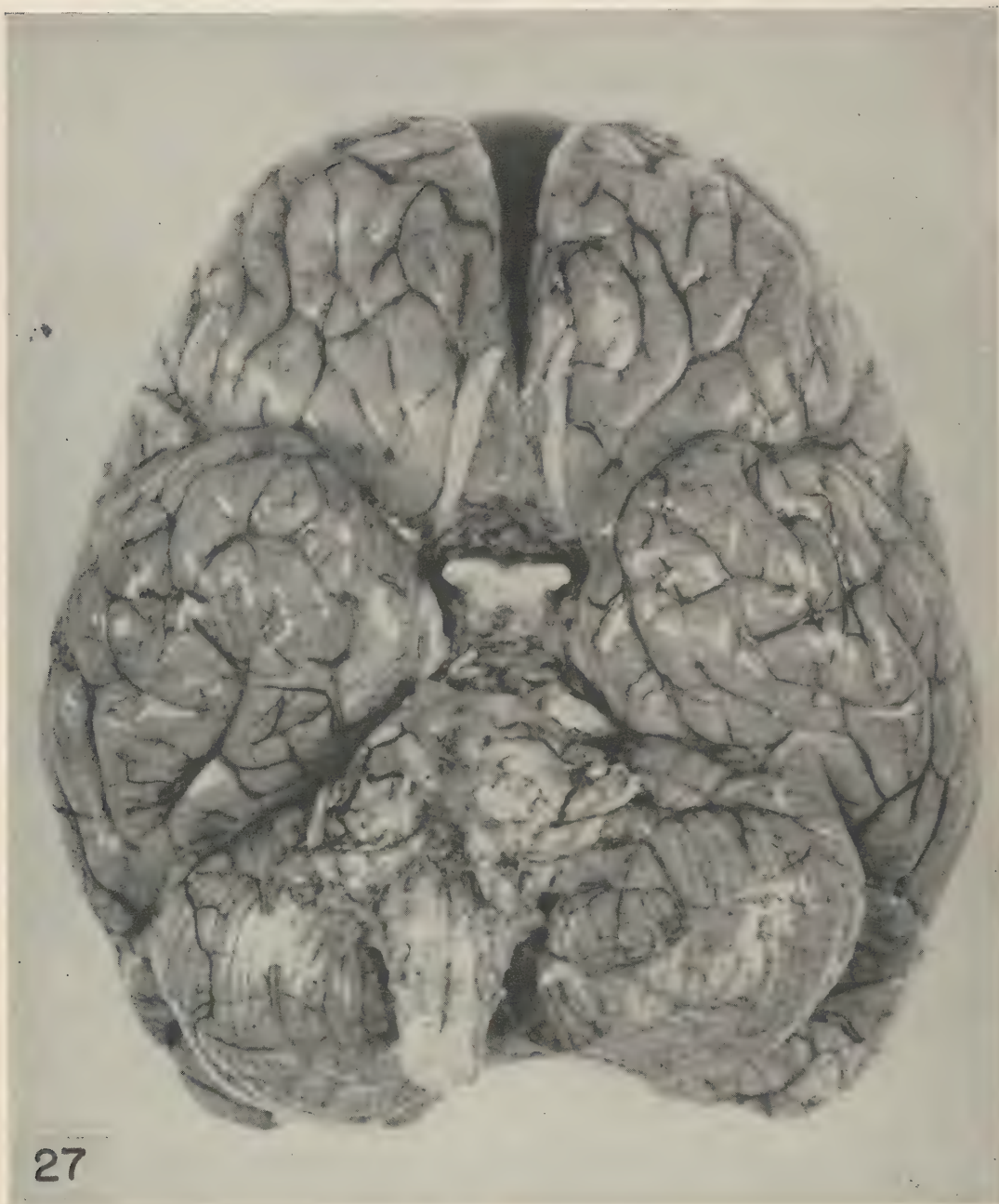


FIG. 27. Disseminated coccidioidomycosis, AIP Ac. 117769: The gross appearance of the plastic type of basal meningitis. Note the dense exudate covering the brain stem, leading to obstruction of the circulation of spinal fluid and internal hydrocephalus. Death after 111 days.

of the brain substance, particularly the brain stem, in a rigid, highly organized, granulomatous mass of tissue (Fig. 27), and 2) a pronounced exudation of fluid with wandering cells and polymorphonuclear leukocytes, which

has undergone only a minimal granulomatous transformation. The more typical reaction to *C. immitis* is the former. A characteristic feature of the granulomatous reaction is the typical tubercle with giant cells which almost

regularly contain the organism; at the same time, many organisms appear free in the exudate. Even in the most highly developed granulomatous reaction one may see, as in other granulomatous lesions, focal areas of suppuration in which there are few organisms and many leukocytes. The thick, plastic, opaque type of alteration of the meninges reminds one of tuberculous meningitis; but the resemblance is only superficial, since the

of our cases the development of a local meningitis about the cord produced all the signs and symptoms of a cord tumor, making necessary an exploratory operation for relief of spinal cord pressure. Such localized spinal leptomeningitis is usually associated with involvement of the dura, which in turn is the result of localization of the infecting agents in the bones surrounding the spinal canal from the blood stream.

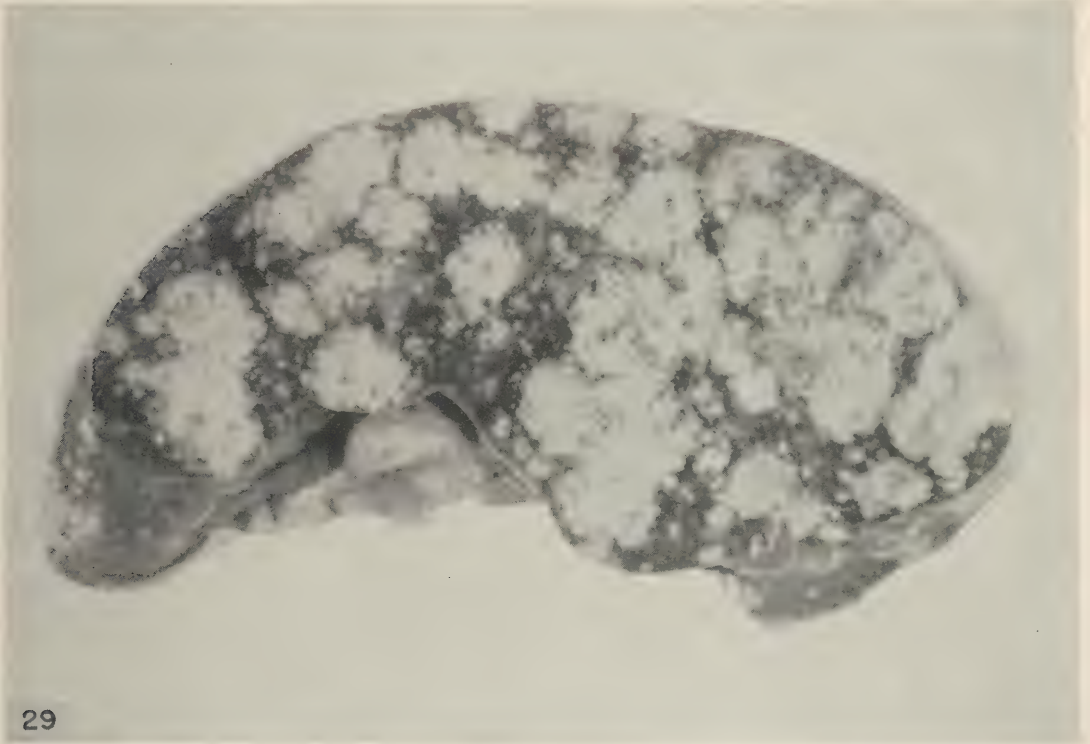


FIG. 29. Disseminated coccidioidomycosis, AIP Ac. 96943: Gross appearance of the spleen. Great numbers of small solitary tubercle-like lesions and great masses of granulomatous tissue. Death after 123 days. This is the same case as seen in Figs. 18 and 22.

degree of thickening and induration of the inflammatory exudate is never so prominent in tuberculous meningitis as in *C. immitis* infection. Due to the reaction in the meninges about the brain stem, the movement of spinal fluid from the brain cavities into the subarachnoid space is obstructed, resulting in extreme grades of hydrocephalus.

Granulomatous meningitis of the spinal cord may occur either with or independent of the infection of the cerebral meninges. In one

Thirteen of the 18 cases of coccidioidal meningitis recorded in this report were previously reported by Schlumberger.²³⁶

It is important to note that coccidioidal meningitis is often the only evidence of dissemination. In a few cases studied at autopsy it has not been possible to locate the primary focus of infection representing the point of entry of the organisms into the circulation, but in most of them the focus of dissemination has been in the lungs. In the cases in which

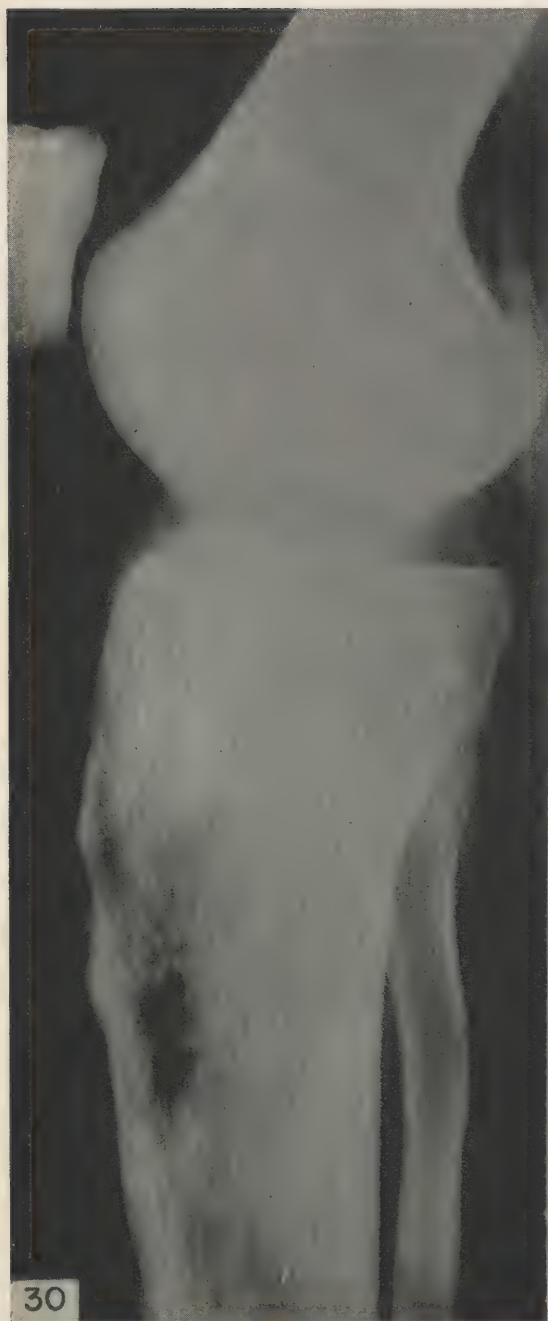


FIG. 30. Disseminated coccidioidomycosis, AIP Ac. 78078: Roentgenogram of lesion of tibia. The bone destruction is more pronounced in the medullary portion, but also involves the cortex. Note also the fuzzy appearance of portions of periosteum. Death in 140 days.



FIG. 31. Disseminated coccidioidomycosis, AIP Ac. 94964: Erosion of vertebral bodies by granulomatous process. Intravertebral cartilage is also involved. Note the resemblance of the lesion seen in Fig. 32.



FIG. 32. Disseminated coccidioidomycosis, AIP Ac. 132016: Roentgenogram of destructive lesion in lower cervical vertebrae. Note the soft tissue involvement and draining sinus in the neck. Death in 177 days.

meningitis is only one of the many evidences of widespread dissemination, there are many foci from which dissemination to the meninges might have occurred. Some of the oldest lung lesions have been found in cases of fatal menin-

infection within the bone. Psoas abscesses, already described, have been seen in several cases of this series. Primary infection of the muscles by lodgement of organisms from the blood stream rarely if ever occurs. In this series of



FIG. 33. Disseminated coccidioidomycosis. Multiple draining sinuses on dorsal and palmar aspects of the wrist. Note the scars on the dorsum of the hand, where previous sinuses have closed.

gitis, coming on many months after the pulmonary disease has become completely asymptomatic. In these old pulmonary lesions, as already noted, there are usually still many organisms that show active propagation; and so the old, presumably healed foci are not infrequently the source of a much-delayed fatal dissemination.

9. *The Voluntary Muscles.* The voluntary muscles adjacent to joints and overlying bony prominences are often involved by extension of the coccidioidal process from the disseminated

cases we have seen no examples of this form of muscle involvement.

10. *The Gastro-intestinal Tract.* It has long been known that infection of the gastro-intestinal tract is most unusual in cases of coccidioidomycosis. In our series the small intestine was not involved in a single instance; however, the peritoneal surfaces of the small intestine have been found to share in the infection of the peritoneal cavity. In one case suppurating masses of lymph nodes ulcerating through the stomach wall gave rise to a granu-

lomatous type of ulceration in the gastric mucosa. In another case a mass of suppurating lymph nodes in the mediastinum extended to involve the esophagus and the trachea, forming a tracheo-esophageal fistula further complicated by extension of the sinuses from the mediastinum into the neck. Direct involvement of the esophagus or of the buccal cavity and its

swallowed in such abundance as they are in pulmonary tuberculosis.

11. *The Genito-urinary Tract.* Lesions have been observed in no other portion of the genito-urinary tract in our cases than the kidney and the prostate. This is in striking contrast to the situation in blastomycosis, in which involvement of the bladder and the

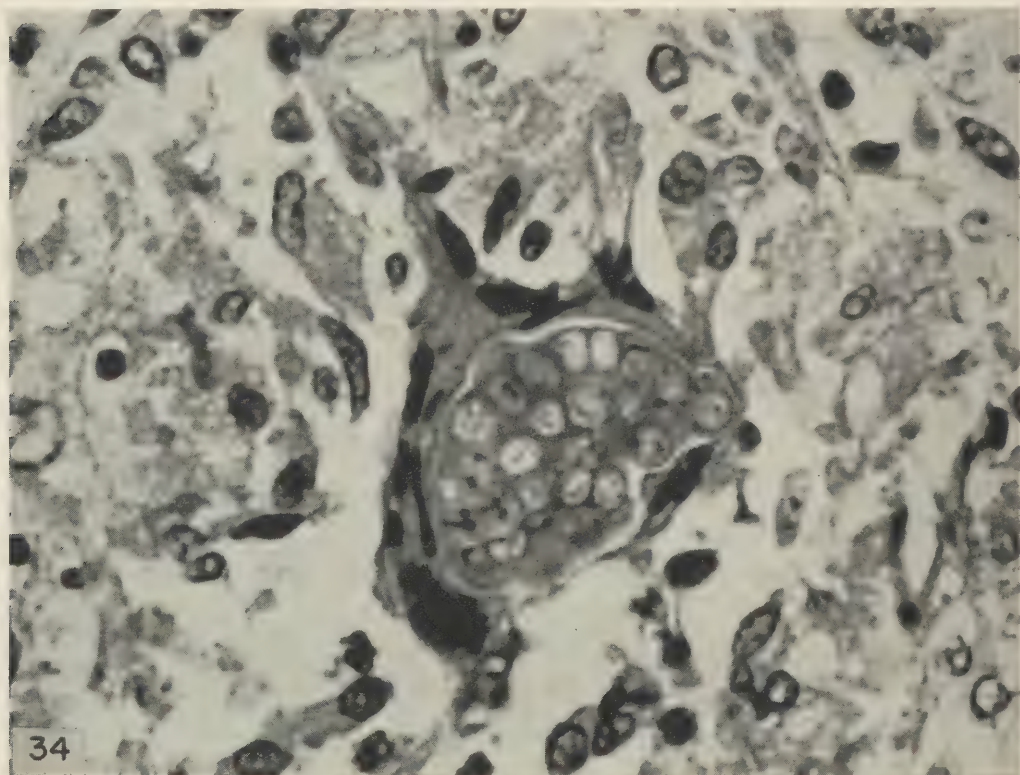


FIG. 34. Forms of *C. immitis* and related histologic response, AIP Ac. 137706: High power magnification of a giant cell containing large organism filled with spores. Note the radial arrangement of the epithelioid cells surrounding the giant cell. Same case as Figs. 6, 19, and 28. ($\times 1000$)

membranes has not been observed in this study.

This striking absence of lesions due to *C. immitis* in the gastro-intestinal tract is a matter of some interest in connection with the pathogenesis of the disease. The extensive pulmonary involvement of coccidioidomycosis is much like that of tuberculosis, but there is no complication in coccidioidomycosis to parallel terminal tuberculous enteritis. The difference may very likely be attributed to the fact that in coccidioid infection of the lung little sputum is produced, and hence organisms are never

ureters and extensive seminal vesiculitis are common. The infrequency of infection of the lower part of the urinary system found in this series of cases seems to be in harmony with previously recorded findings.

VI

THE NATURE AND GENESIS OF THE TYPICAL LESION OF COCCIDIOIDOMYCOSIS

The abundance of histologic material provided by this series of cases of coccidioidomycosis has made it possible to arrive at a

satisfactory understanding of the pathogenesis of the lesion. The character of the lesion, its course, and its outcome appear to be determined by a number of rather specific factors which may be discussed individually, as follows:

A. The Chemotactic Properties of *Coccidioides immitis*

During the development of the coccidioidal lesion the organism appears in the tissues in

spherules. From the endospores develop the next generation of spherules in the tissues, or, in the external environment, the mycelial phase of the life cycle of this organism (Fig. 1). This organism never appears in the tissues in mycelial form except when large open cavities exist. Hyphae then may be found in a cavity. Even this is exceptional and has not been described in the literature. In only one of our cases were hyphae observed (Fig. 11).

The chemotactic properties of the chlam-

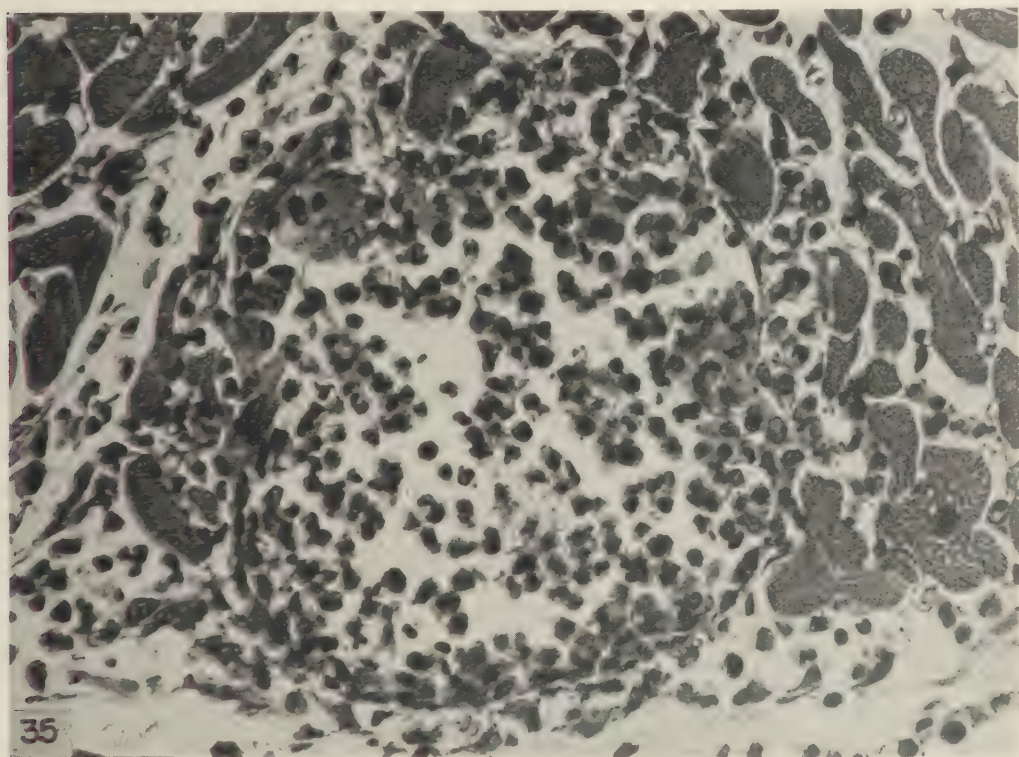


FIG. 35. Forms of *C. immitis* and related histologic response, AIP Ac. 74661: High power magnification of a focal abscess found in the heart muscle. The lesion has formed around a cluster of endospores seen centrally in the lower pole of the lesion. Same case as Fig. 17. ($\times 200$)

a variety of forms, each very likely possessing its own peculiar chemotactic properties. The forms of the organism that appear in the tissues are: 1) the chlamydo-spores, which are developed in the hyphae through a fairly simple process of sporulation, described in detail by Ophüls and Moffit³; 2) the spherules in all of their various developmental stages; and 3) the endospores resulting from endosporulation, which represents the maturation of the

ydospores have not been accurately determined. It is this form of the organism that produces the original infection in the lung or in other tissues, where it is introduced from the external environment. All of our cases are far too advanced for the material at our disposal to give any indication as to the specific cellular response to the presence of the chlamydo-spores. It is well known that once the infection is established, the chlamydo-spores are never again

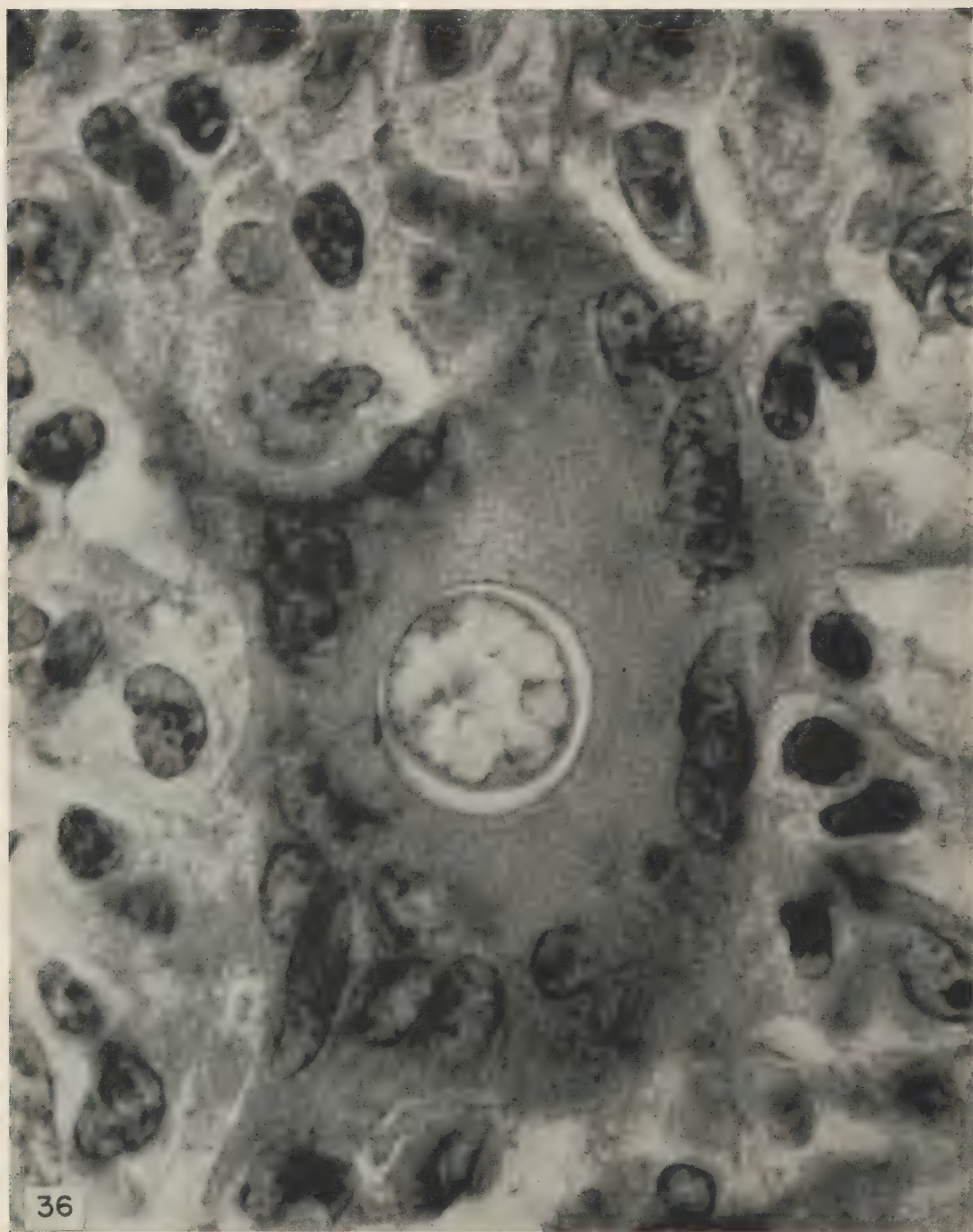


FIG. 36. Forms of *C. immitis* and related histologic response, AIP Ac. 46988: Biopsy of ulcer on lower lip. Large organism engulfed by a giant cell as seen under oil-immersion. The spherule has just begun to form spores. Note the epithelioid reaction surrounding the giant cell. ($\times 2400$)

seen in the tissues, because the mycelial phase of the life cycle of this organism does not develop except in the external environment. Only in the articles of Cronkite and Lack¹⁷⁰ and of Tager and Liebow²⁰⁷ have we found observations relating to the pathogenesis of the lesions produced by chlamydospores. Since these forms, at least morphologically, somewhat resemble the spores produced by the developing spherules in the tissues, it may be that the reaction to the chlamydospores will prove to be identical with that to the endospores.

The spherules in the intermediate developmental stages appear in the tissues in varying numbers. In some cases they are abundant, and in others so scarce as to be very difficult to find. Regardless of the number of organisms, however, it appears that the cells attracted by these forms of the parasites are the mononuclear wandering cells (Fig. 18) which accumulate in great abundance and almost completely replace the polymorphonuclear leukocytes, which dominate the histologic field in the earliest stages of the development of the lesion (when the organisms are of the spore form). These mononuclear wandering cells undergo morphologic and functional changes which eventually give to the mature lesion its characteristic granulomatous features.

The mature, sporulating spherules possess a combination of properties of the endospore and the immature spherule as regards their attraction for reacting cells (Fig. 37). However, the moment the mature spherule ruptures its capsule, thus exposing to the tissues the endospores, the polymorphonuclear leukocytes gather about the structure in great numbers. It is a rather fascinating experience to observe the regularity with which the polymorphonuclear leukocytes seem to rush to the endospore-forming organisms and actually invade the ruptured capsule of the mature organism the moment the endospores become accessible. After the sporulating spherule has emptied itself, the polymorphonuclear leukocytes often very nearly fill it. The capsular substance seems to possess, however, little attraction for these cells; empty capsules are commonly ob-

served in the tissues where organisms are present in great numbers and maturing rapidly. These broken-up membranes may sometimes be seen surrounded by macrophages of the type that usually phagocytize the intact spherules.

The endospores, as will be seen from the accompanying diagram representing the life history of this parasite (Fig. 1), are about the size of an ordinary neutrophilic leukocyte or slightly smaller. These very early forms of the developing parasite are extruded from the mature sporulating spherule into the tissues, where they provoke a characteristic cellular response. The organisms at this stage are extremely difficult to find in the sections, but they may be seen when stained properly. They possess a high degree of attraction for the polymorphonuclear leukocytes of the neutrophilic variety; and so, surrounding these forms of the parasite, there regularly develops a little focus almost exclusively composed of these cells (Fig. 35). Many of the endospores, when they are just released from the spherules, possess no capsule at all or very poorly developed ones. The polymorphonuclear leukocytes attempt to phagocytize the spores, but this is not often successful. Either the organisms are too large or their toxic effects interfere with the process of phagocytosis. After the spore has grown considerably, particularly after the capsule appears to have become well formed, the endospores possess also a certain attraction for the large mononuclear wandering cells. It is this form of the organism that one sees most often within the cytoplasm of the large mononuclear wandering cells.

B. The Capacity of the Organisms to Injure Tissues

The ability of the organisms in their various forms to destroy tissue determines the degree of necrosis, as well as the amount of exudation of fluid from the blood vessels as the lesion develops. Presumably the chlamydospores, and certainly the tissue forms of the parasite that develop immediately from chlamydospores, are capable of injuring the blood vessels as indicated by the marked extravasation of fluid in

the earliest reaction to the endospores in the tissues. Organisms in this stage of their development also are highly capable of destruction of the cells of the inflammatory exudate. This is observed in little foci of polymorphonuclear leukocytes that appear about the endospores. These cells quickly show evidences of injury, and eventually are killed outright. This destructive process is indicated by the presence of great masses of cellular debris in the early lesions, also by the characteristic staining reactions of the dying and injured leukocytes. Further evidence of the capacity of the spores to injure tissue is the hemorrhagic character of the exudate in the early stages of the development of the infection, especially in the lung.

In view of the power of the organisms to kill living cells, it is remarkable that the fixed tissues, with the exception of the blood vessels, suffer only a limited degree of injury. This explains the complete restoration which so often occurs in the primary pulmonary form of coccidioidomycosis. In certain exceptional cases massive destruction of the fixed tissues does take place. Exactly what factors are responsible for this necrotizing effect is difficult to determine. The actual number of spherules in the tissues may be a dominating influence, since the most highly necrotizing lesions that we have observed are those in which the organisms are present in abundance. What is probably more significant is that they are in the maturing sporulating phase of their development (Figs. 16 and 17). It is not unusual to see masses of organisms in the intermediate stages of development lying in tissues in which virtually no necrotizing effect can be seen (Fig. 37). Thus, while the number of organisms concerned is undoubtedly of importance in determining the character and outcome of the lesion, the main factor is more likely the stage of development of the parasite.

C. The Sensitization Factor in Coccidioidal Infection

The materials at our disposal have not made it possible for us to determine exactly what role the sensitization to products of grow-

ing *C. immitis* may play in the pathogenesis of the disease. There is no question that the tissues do become sensitized and, when brought into contact with culture filtrates of *C. immitis*, do react violently, even to the extent of becoming extensively necrotic. This is a matter, however, which requires discriminating experimental observation, and cannot be settled by clinical or anatomic techniques. In cases in our series highly necrotizing lesions have developed in individuals giving no skin reaction whatever to coccidioidin; and, in contrast, very widespread lesions, especially in the lung, with virtually no necrosis, have been seen in individuals highly sensitive to coccidioidin. In this connection we have repeatedly made the observation that extensive necrosis of the lesions may have taken place in certain areas of the body, while lesions in other areas may be intact. This would seem to indicate that, if a sensitization factor is involved in the development of coccidioidal lesions, it is local, and not general.

D. Intracellular Ferments and Other Factors

In lesions which become necrotic, subsequent changes may result either in liquefaction of the necrotic material or in its persistence in a coagulative form (Figs. 24, 25, and 26). According to our observations, liquefaction occurs chiefly in those areas where the polymorphonuclear leukocytes have been dominant in the inflammatory exudate. It has not been a prominent feature in those lesions in which the inflammatory exudate is composed chiefly of mononuclear wandering cells and their products of development.

Lesions characterized by the epithelioid reaction tend to remain intact insofar as the fundamental structural pattern is concerned, as seen so well in some of the very old residual lesions in the lung. The necrotic tissue often reveals the original pattern of the lung, as is so often the case in the gummatous lesions of syphilitic infection (Fig. 18). Although it is a natural assumption that this difference in the outcome of the necrotizing process is the result of the character of the ferments in-

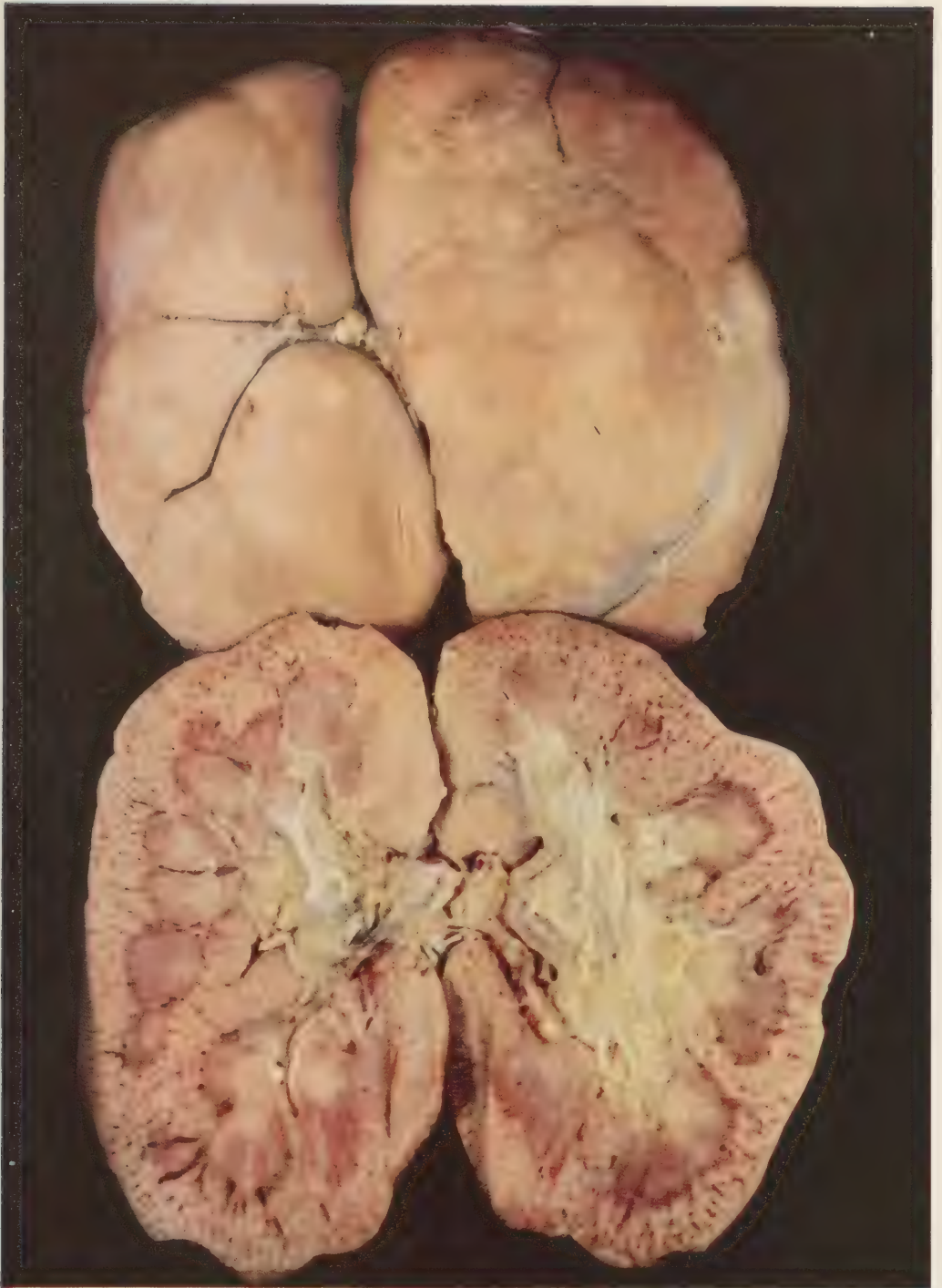


FIGURE 28. Disseminated coccidioidomycosis, AIP Acc. 133706: The gross appearance of disseminated kidney lesions. Note the yellow granulomatous nodules distributed over the outer cut surfaces involving both cortex and medulla. This is the same case as Figs. 6 and 19.

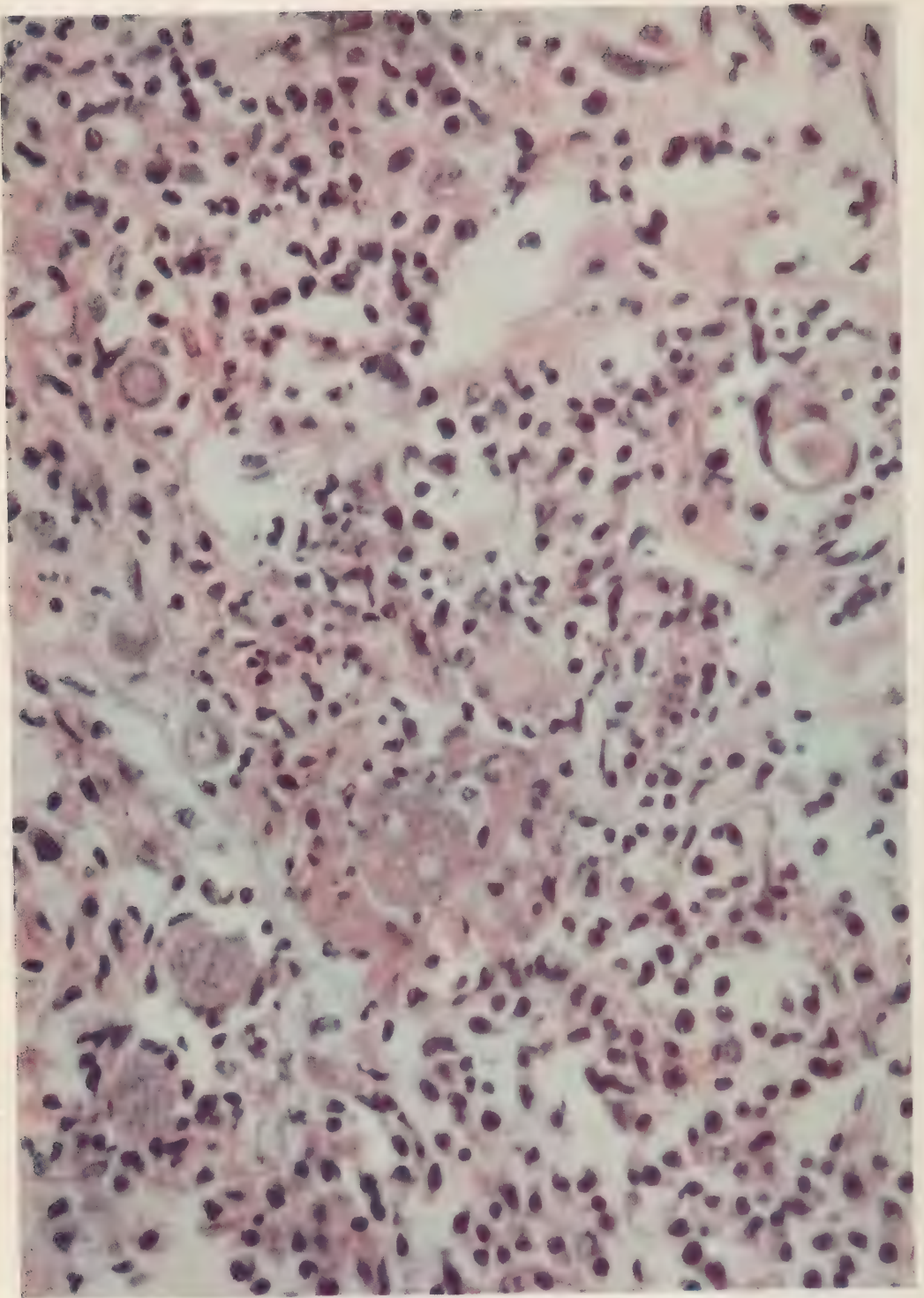


FIGURE 37. Forms of *C. immitis* and related histologic response. Section of lung showing great number of organisms in different stages of development. Note the macrophage crowded with organisms, 4 in spherule form and 1 almost endosporulating. The tissue reaction is of the mixed granulomatous type.

volved or actually produced by the cells of the inflammatory exudate, our own studies in this series have not made it possible to substantiate such a supposition. Reasoning by analogy, however, it seems that we may be reasonably sure that the ferments produced by the polymorphonuclear leukocytes are chiefly responsible for the liquefactive form of necrosis seen in almost all the large disseminated lesions of coccidioidomycosis. However, undoubtedly there are other factors involved in the process, and the matter of judgment must be left open for settlement through experimentation. Nothing we have seen in our study of this series of cases or in reviews of former studies gives any indication that products of the organisms themselves influence in one way or another the development of liquefaction following necrosis of the tissues.

E. The Proliferative (Stimulative) Factor

One of the most striking features of the reaction to *C. immitis* is the proliferation of the wandering cells of the exudate and their transformation into large epithelioid elements and giant cells (Figs. 20, 23, 34, 36, and 37). The stimulus for this growth response is related directly to the organisms, as indicated by the observation that the large mononuclear cells begin to grow and reproduce as soon as they engulf the organisms. They increase in size and the nuclei multiply (Figs. 34 and 36); the end result is the formation of the large giant cells. These changes do not occur in those mononuclear cells not in intimate contact with the organisms. The growth-stimulating influence of the parasite seems to affect chiefly the cells of the exudate, almost never the cells of the tissues. In the lungs, for example, the reaction develops beautifully within the alveolar spaces, while the alveolar walls remain virtually unchanged (Fig. 18). There would, therefore, seem to be some peculiar affinity between the parasites and the large mononuclear cells. The regularity with which the parasites are seen within these cells suggests that they may actually grow best in an intracellular position, just as do the filtrable viruses and certain other disease agents. Al-

though it is clear that in the case of *C. immitis* obligate intracellular parasitism does not exist, an intracellular location may be most favorable for the propagation of these fungi and for the development of the characteristic reaction. *C. immitis* may thus be placed among the facultative intracellular parasites. It may be that an intracellular environment is essential for the development of a certain stage in the life cycle of this fungus, and that the large mononuclear cells serve as hosts during this phase.

F. Correlation of Pathogenic Factors and the Development of the Typical Lesion

If one gives due consideration to the various factors involved in the production of lesions by *C. immitis*, there is no difficulty in understanding the rather complex character of coccidioid lesions. It is customary to describe the lesion as a granuloma; and in certain phases of its development the reaction is indeed strictly granulomatous, that is, it is a lesion resulting from the response of the mononuclear cells to the presence of the fungus. Unfortunately, however, the reaction of the body to *C. immitis* is not so simple as this; instead, it is a combination of reactions, both granulomatous and suppurative.*

In the cases that we have studied the extrapulmonary disseminated lesions have usually been chiefly suppurative; the pulmonary lesions, on the contrary, have been predominantly granulomatous. It is never possible, however, to classify these lesions as strictly of one type or another because histologically they are all combinations of both. The gross character of the lesions naturally depends upon the predominance of one type of reaction; nevertheless, it is possible to trace a characteristic sequence in the development of the "typical" lesion that results from *C. immitis* infection.

* The distinctions between granulomatous and suppurative inflammatory reactions emphasized here have been discussed in detail in the following references: (1) Forbus, Wiley D.: *Reaction to Injury, Pathology for Students of Disease*, Chapters VI and XXVI; (2) Forbus, Wiley D.: *The Nature and General Pathological Significance of Granulomatous Inflammation*, *American Lecture Series*, Charles C Thomas (in press).

The primary lesion in the lung may be taken as an example. The introduction of chlamydospores into the pulmonary alveoli arouses an immediate polymorphonuclear leukocyte reaction, the resulting picture being indistinguishable from pneumonic consolidation of bacterial origin (Figs. 12, 13, and 14). Growth of the chlamydospores and their conversion to spherules, which are the typical forms of the parasite in the tissue, are accompanied by an influx of great numbers of mononuclear wandering cells. These cells surround and envelop the tiny organisms to serve as their intimate hosts (Fig. 18). The spherule undergoes progressive growth and development within the cytoplasm of the mononuclear cell until it reaches the stage of endosporulation. By this time the parasitized cell has been transformed into a large mononucleated giant cell (Figs. 34 and 36). Other macrophages, some parasitized and some not, proliferate, thus substituting a typical mononuclear or epithelioid reaction (Figs. 23, 34, and 36) for the original polymorphonuclear leukocyte exudate. The maturation of the spherules, the development of the endospores, and their discharge from the mother spherule result in the destruction of the large parasitized giant cell with dissemination of the endospores into the tissue spaces. Maturation of the spherules takes place extracellularly at the same time. The liberated endospores immediately attract polymorphonuclear leukocytes to the scene, the result being the formation of minute suppurative foci (Fig. 35). The endospores are very difficult to see in the tissues in ordinary sections, but great numbers of spherules in various stages of development are readily visible. This combination of suppurative foci and mononuclear and epithelioid or genuine granulomatous reaction constitutes the usual picture met with in the histologic study of this disease (Fig. 17). Ultimately, either the lesion becomes necrotic and liquefies (Figs. 24, 25, and 26) or necrosis is followed by gradual hyalinization of the granulomatous tissue. Scarring results from the healing of either type of lesion. In few of the lesions which we have seen, even those of the longest duration, has significant calcification

occurred. In conclusion it should be emphasized again that, once the lesion reaches the advanced granulomatous state, complete resolution without residual changes in the tissue no longer is possible. Thus, in primary pulmonary coccidioidomycosis of the type which heals without residual changes, the reactions must necessarily have been of the ordinary polymorphonuclear or very early mononuclear exudative variety.

VII

COMMENT

The study of this collection of 95 cases of coccidioidomycosis, all of the disseminated type, has presented an opportunity for further investigation of the clinicopathologic problems of the disease in the light of the developments of recent years. We have made use of this opportunity by attempting to solve some of the problems utilizing materials which, up to this time, have not been available. We have been especially interested in the pathogenesis of the primary pulmonary form of this disease, the pathologic anatomy of which has remained quite unexplored because recovery is the rule in coccidioidomycosis restricted to the lungs. Although the material at our disposal has come from cases of the disseminated form of coccidioidomycosis, we have been able to construct, according to well-established pathologic principles, the probable pulmonary reactions to the primary infection with *C. immitis*. In this study, beyond the simple matter of placing on record a large series of carefully studied cases, we have hoped, among other things, to discover data upon which to base a more accurate prognosis of the disease, particularly with respect to the cases of coccidioidomycosis in the armed forces. It is evident from our study that disseminated coccidioidomycosis will continue to occur among those who have served in the armed forces for perhaps as long as ten years. These cases will represent recrudescences of quiescent coccidioidal infection incurred in endemic areas. Undoubtedly a high percentage of these will be in the nature of widespread dissemination of coccidioidal lesions, and the mortality will be considerable.

This is a problem for the medical profession as a whole, since the men who have been exposed to *C. immitis* infection will be scattered throughout the country, and the recognition of the disease will be the responsibility of the local practitioner. Although the problem in the case of the veteran will not be a large one and will be definitely restricted as to duration, it will be a matter of considerable importance to the government.

In this study the nature of the materials dealt with has not made it possible to contribute materially toward the solution of the problem of the mode of infection in man, particularly as regards the epidemiologic aspects of the problem. What we have learned certainly supports the previously held opinion that man-to-man infection is of no material importance. Whether or not man receives his infection from a reservoir in nature consisting of infected small wild animals, particularly rodents, has not been established. The belief that man is infected, almost without exception, through inhalation of the spores of this fungus receives considerable support from our observations regarding the primary pulmonary form of this disease. Since men do not infect each other with *C. immitis*, it is reasonable to believe that there is no great likelihood of the spread of this disease into areas where it is not endemic. On the other hand, it is conceivable that infected human beings, of which there are now a great number, may be the means through which the organisms may be spread to places where the conditions are favorable for their propagation in the outer environment. From what is known about the organism and its life in the outer environment, however, it is improbable that this constitutes a serious threat.

An important aspect of the problem of coccidioidomycosis of current interest is the confusion of residual coccidioidal lesions in man with residual tuberculous lesions. The studies of Aronson and associates^{186,187} and others seemed to indicate that a considerable number of calcified foci in the lungs believed to be of tuberculous origin might be due to *C. immitis* infection. Little support was found

for this idea in the 95 cases of our series since instances of residual calcification of the lungs were rarely observed. Although the problem obviously needs further study, our experience offers little encouragement to those who would attribute to coccidioidal infection the residual calcifications so frequently discovered in the lungs in the absence of a positive tuberculin reaction.

Although extensive histopathologic studies have not brought forth data which would remove coccidioidal infection from the category of granulomatous disease, it has become apparent that, like certain other fungus infections, coccidioidomycosis belongs to a pathogenic type of infectious disease that lies somewhere between the purer forms of granulomatous infection represented by tuberculosis and the genuinely suppurative infections produced by the more common pyogenic bacteria. Ample justification for the intermediate classification of this disease will be apparent to anyone who devotes himself seriously to the study of the pathogenesis of the great variety of lesions which characterize coccidioidomycosis as it develops from the earliest stages of infection to the widely disseminated and highly complicated gross and histologic expressions of the terminal process.

VIII

SUMMARY AND CONCLUSION

1. A study of 95 cases of the disseminated form of coccidioidomycosis occurring in the armed forces between 1941 and 1946 has been made with particular reference to the pathogenesis of the disease. Fifty of these were fatal cases studied comprehensively clinically and at autopsy. Forty-five cases were studied clinically and by biopsy.

2. The analysis of this group of cases appears to justify the following statements:

a. Coccidioidomycosis is primarily and predominantly a pulmonary disease, the mortality of which is negligible. When death occurs, it is always associated with an endogenous reinfection, that is, the disseminated form of the disease.

b. Coccidioidomycosis is a granulomatous

infectious disease with pathogenic and pathologic-anatomic characteristics which place it between the typical granulomatous disease, as represented by tuberculosis, and the typical acute suppurative infectious disease, as represented by the ordinary pyogenic infections.

c. Coccidioidomycosis occurs in two clinico-pathologic forms:

- (1) Primary pulmonary coccidioidomycosis, occurring in subclinical and clinical forms—the primary infection complex, and
- (2) Endogenous reinfection coccidioidomycosis, the secondary disseminated or generalized infection.

d. Primary pulmonary coccidioidomycosis in its mildest, often subclinical, forms is represented anatomically by essentially non-granulomatous inflammation of the lung of either a focal or diffuse character, accompanied by bronchial and mediastinal acute lymphadenitis and, in a certain percentage of the cases, erythema nodosum. In its severe, clinically obvious form genuine suppurative and granulomatous lesions develop; these are sometimes highly destructive, resulting in the formation of pulmonary cavities.

e. Primary pulmonary coccidioidomycosis usually heals completely without residual pulmonary lesions, but the rare suppurative and granulomatous necrotizing lesions always heal by scar formation. Calcification of these lesions is not common.

f. Reinfection pulmonary coccidioidomycosis may arise by intrapulmonary or extrapulmonary bronchial ulceration and aspiration of infected exudate, or by vascular dissemination of organisms from both intra- and extrapulmonary sources.

g. Secondary or disseminated coccidioidomycosis may, and frequently does, develop during the active progress of the primary pulmonary infection.

h. Clinically completely healed but residual pulmonary lesions contain vegetative organisms in all stages of development. These may serve as the source of disseminated infection months or years after the pulmonary disease has disappeared.

i. The ten most frequent sites of the lesions resulting from dissemination of *C. immitis* by the blood stream are, in order, as follows:

- (1) the lungs
- (2) the lymph nodes
- (3) the spleen
- (4) the skin and subcutaneous tissues
- (5) the liver
- (6) the kidney
- (7) the bones
- (8) the meninges
- (9) the adrenal
- (10) the myocardium

j. The characteristic reaction of the body to *C. immitis* is purely inflammatory; the reaction may be (1) suppurative, the reacting cells of the exudate being predominantly polymorphonuclear neutrophilic leukocytes, or (2) granulomatous, the reacting cells of the exudate being predominantly large mononuclear wandering cells ("reticulo-endothelial cells," "monocytes," "histiocytes," "tissue macrophages") and their epithelioid and giant cell derivatives, or (3) mixed, in which the suppurative and granulomatous reactions are about equally distributed.

k. The histologic character of the inflammatory reaction varies greatly in any given lesion, and from lesion to lesion in the same individual, and appears to be determined chiefly by the number and the developmental stage of the organisms present in the lesion. The factor of sensitization of the individual to coccidioidin does not appear to be material.

l. Absolute diagnosis of coccidioidomycosis can be made solely upon demonstration of the organisms in the tissues, exudate, or body fluids. This can be done in virtually all cases by microscopic examination. Cultures or animal inoculations are rarely required when tissues can be obtained for study.

m. It is unlikely that the healing of pulmonary coccidioidomycosis is responsible for the presence of focal calcification of the lungs in any significant proportion of the cases showing this lesion in the absence of a positive tuberculin reaction.

n. Disseminated endogenous reinfection will continue to occur among the members of

the armed forces who were trained in the endemic areas of the Southwest for approximately ten years, and will cause a number of deaths.

o. It does not appear likely that coccidioidomycosis will spread to non-endemic areas as a result of the migration of members of the armed forces who were exposed to this disease during training in endemic areas.

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LITERATURE

1892

¹Wernicke, R.: Über einen Protozoenbefund bei Mycosis fungoides, Zentralbl. f. Bakt. 1892, 12:859.

1896

²Rixford, E., and Gilchrist, T. C.: Two cases of protozoan (coccidioidal) infection of the skin, Reports Johns Hopkins Hosp. 1896, 1:209.

1900

³Ophüls, W., and Moffit, H. C.: A new pathogenic

mould (formerly described as protozoon "*Coccidioides immitis pyogenes*"), Phila. M. J. 1900, 5:1471.

⁴Posadas: Psorospermiose infectante généralisée, Rev. de chir., Paris, 1900, 20:275.

1904

⁵Wolbach, S. B.: The life cycle of the organism of dermatitis coccidioides, J. Med. Res. 1904, 13:53-60.

1905

⁶Ophüls, W.: Coccidioidal granuloma, J.A.M.A. 1905, 45:1291-1296.

⁷Ophüls, W.: Further observations on a pathogenic mould formerly described as a protozoon (*Coccidioides immitis*, *Coccidioides pyogenes*), J. Exper. Med. 1905, 6:443.

1906

⁸Brown, P. K.: Report of fifteenth and sixteenth cases of coccidioidal granuloma, California State J. M. 1906, 4:324-326.

1907

⁹Hektoen, L.: Systemic blastomycosis and coccidioidal granuloma, J.A.M.A. 1907, 49:1071-1077.

1909

¹⁰Evans, N.: Coccidioidal granuloma and blastomycosis in the central nervous system, J. Tennessee Med. Assn. 1909-1910, 2:166-174.

1912

¹¹von Wasielewski: *Coccidioides immitis*, Deutsche med. Wchnschr. 1912, 38:2341.

1913

¹²MacNeal, W. J., and Hjelm, C. E.: Note on a mold, *Coccidioides immitis*, found in a case of generalized infection in man, J.A.M.A. 1913, 61:2044.

1914

¹³Brown, P. K., and Cummins, W. T.: A differential study of coccidioidal granuloma and blastomycosis; pathology and bacteriology, report of two additional cases of coccidioidal disease, Tr. Assn. Am. Phys. 1914, 29:628-650.

¹⁴Cooke, J. V.: Immunity tests in coccidioidal granuloma, Proc. Soc. Exper. Biol. & Med. 1914-15, 12:35.

¹⁵MacNeal, W. J., and Taylor, R. M.: *Coccidioides immitis* and coccidioidal granuloma, J. Med. Res. 1914, 30:261-274.

1915

¹⁶Campiche, P.: The Californian blastomycosis (*oidium coccidioides*), Rev. Med. Suisse Rom. 1915, 35:769-779.

¹⁷Dickson, E. C.: Oidiomycosis in California with especial reference to coccidioidal granuloma, including nine new cases of coccidioidal granuloma and

one of systemic blastomycosis, *Arch. Int. Med.* 1915, 16:1028-1044.

1920

¹⁸ Lynch, K. M.: Coccidioidal granuloma including the first reported case east of the Mississippi, *South. M. J.* 1920, 13:246.

1923

¹⁹ Hirsch, E. F.: Introduction of coccidioidal granuloma into Chicago, *J.A.M.A.* 1923, 81:375-377.

²⁰ Taylor, R. G.: Coccidioidal granuloma, *Am. J. Roentgenol.* 1923, 10:551.

1924

²¹ Gomes, J. M., and deAssumpsao: En tourno de genero coccidioides, *Ann. paulist. de med. e cir.* 1924, 15:49-61.

1925

²² Bump, W. S.: Observations on the growth of *Coccidioides immitis*, *J. Infect. Dis.* 1925, 36:561-565.

²³ Montenegro, J.: Septicemia by *Coccidioides immitis*, *Brasil-med.* 1925, 39:69.

²⁴ Riesman, D., and Ahlfeldt, F. E.: Coccidioidal granuloma, *Tr. Assn. Am. Phys.* 1925, 40:300-307.

²⁵ Rocha Lima: Histopathologie der exotischen Blastomykosen, *Verhandl. d. deutsch. path. Gesellsch.* 1925, 20:342-353.

1926

²⁶ Ahlfeldt, F. E.: Studies in coccidioidal granuloma, mode of infection, *Arch. Path.* 1926, 2:206-216.

²⁷ Proescher, F., Ryan, F., and Krueger, A. P.: Case of coccidioidal granuloma with autopsy findings, *J. Lab. & Clin. Med.* 1926, 12:57-70.

1927

²⁸ Castellani, A.: Fungi, *Arch. Dermat. & Syph.* 1927, 16:383, 571, 714.

²⁹ daFonseca, O., and deArea Leao, A. E.: Complement deviation in coccidioidal granuloma; sensitivity of filtrate from culture of *Coccidioides immitis* used as antigen, *Scienza med.* 1927, 5:682-683.

³⁰ daFonseca, O., and deArea Leao, A. E.: Specific cutaneous reaction of filtrate from culture of *Coccidioides immitis*, *Compt. rend. Soc. de biol.* 1927, 97:1796-1797.

³¹ Delore, P., and Rosette, M.: Tuberculose et mycoses, *J. de med. de Lyon* 1927, 8:205, 231.

³² deSonzá Campos, E., and deAlmeida, F. P.: Coccidioidal granuloma; 10 cases at Sao Paulo, *Ann. Fac. de med. da Univ. de S. Paulo* 1927, 2:203-220.

³³ Guy, W. H., and Jacob, F. M.: Granuloma coccidioides, *Arch. Dermat. & Syph.* 1927, 16:308-311.

³⁴ Hirsch, E. F.: Skin reactions with coccidioidal granuloma, *Tr. Chicago Path. Soc.* 1923-27, 12:335.

³⁵ Hirsch, E. F., and Benson, H.: Specific skin and testis reactions with culture filtrates of *Coccidioides immitis*, *J. Infect. Dis.* 1927, 40:629-633.

³⁶ Hirsch, E. F., and D'Andrea, D.: Specific substance of *Coccidioides immitis*, *J. Infect. Dis.* 1927, 40:634-637.

³⁷ Jacobson, H. P.: Granuloma coccidioides, apparently successfully treated with colloidal copper; 2 cases, *California and Western Med.* 1927, 27:360-364.

³⁸ Kelton, W.: Coccidioidal granuloma, *Northwest. Med.* 1927, 26:92-93.

³⁹ Riesman, D., and Ahlfeldt, F. E.: Coccidioidal granuloma, review of clinical data with report of a Pennsylvania case, *Am. J. M. Sc.* 1927, 174:151-167.

⁴⁰ Shear, C. L.: Mycology in relation to human pathology, *Am. Naturalist* 1927, 61:151-159.

1928

⁴¹ Castellani, A.: Blastomycosis and some other conditions due to yeastlike fungi (budding fungi), *Am. J. Trop. Med.* 1928, 8:379-422.

⁴² daFonseca, O., and deArea Leao, E. A.: Coccidioidal granuloma; forms of development of the parasite in the tissues, in most of the lymph nodes, and in cultures; systematic position of *Coccidioides immitis*, *Compt. rend. Soc. de biol.* 1928, 98:619-621.

⁴³ deArea Leao, A. E.: More rapid development of *Coccidioides immitis* in culture media to which filtrates of other cultures of the microorganism have been added (vaccinated cultures), *Compt. rend. Soc. de biol.* 1928, 99:883-884.

⁴⁴ Jacobson, H. P.: *Coccidioides granuloma*, *Calif. & West. Med.* 1928, 29:392-396.

⁴⁵ Jacobson, H. P.: Coccidioidal granuloma, specific, allergic, cutaneous reaction, experimental and clinical investigations, *Arch. Dermat. & Syph.* 1928, 18:562-567.

⁴⁶ Kogoj, F.: Hematogene Dermatomykosen nach subcutäner und intramuskulärer Infektion, *Arch. f. Dermat. u. Syph.* 1928, 154:463-475.

⁴⁷ Stark, N. A., and Becker, F. E.: Coccidioides granuloma, case, *Colorado Med.* 1928, 25:196-202.

⁴⁸ Tomlinson, C. C.: Coccidioides granuloma, *M. Clin. North America* 1928, 12:457-462.

⁴⁹ Tomlinson, C. C., and Bancroft, P.: Coccidioides granuloma, case responding favorably to antimony and potassium tartrate, *J.A.M.A.* 1928, 91:947-951.

⁵⁰ Walters, P. R.: Coccidioides granuloma, case, *California & West. Med.* 1928, 29:188-189.

1929

⁵¹ Ahlfeldt, F. E.: Special observations on morphology of *Coccidioides immitis*, *J. Infect. Dis.* 1929, 44:277-281.

⁵² Beck, M. D.: Occurrence of *Coccidioides immitis*

in lesions of slaughtered animals, *Proc. Soc. Exper. Biol. & Med.* 1928-29, 26:534-536.

⁵³ Burgess, J. F.: Coccidioidal granuloma, case, *Brit. J. Dermat.* 1929, 41:145-148.

⁵⁴ Cummins, W. T., Smith, J. R., and Halliday, C. H.: Coccidioidal granuloma; epidemiologic survey with report of 24 additional cases, *J.A.M.A.* 1929, 93:1046-1049.

⁵⁵ daCosta, A. F., Jr.: Treatment of coccidioidal granuloma by gold-salts, case, *Brasil-med.* 1929, 43:1400-1402.

⁵⁶ DeAlmeida, F. P.: Comparative study of coccidioidal granuloma in United States and Brazil, *Ann. Fac. de med. de Sao Paulo* 1929, 4:91-98.

⁵⁷ Dickson, E. C.: Mimicry of tuberculosis by coccidioidal granuloma, *Tr. Assn. Am. Phys.* 1929, 44:284-294.

⁵⁸ Evans, N., and Ball, H. A.: Coccidioidal granuloma, analysis of 50 cases, *J.A.M.A.* 1929, 93:1881-1885.

⁵⁹ Jacobson, H. P.: Coccidioidal granuloma; further observations with report of seven additional cases, *M. J. & Rec.* 1929, 130:424-498.

⁶⁰ Kadisch, E.: Beiträge zur Lehre von den Dermatomykosen; Über den Verbleib intrakardial injizierten Pilzmaterials beim Meerschweinchen, *Arch. f. Dermat. u. Syph.* 1929, 158:349-353.

⁶¹ Kalichman, G. S., and Madsen, L. J.: Coccidioidal granuloma, case, *California & West. Med.* 1929, 31:141-142.

⁶² Lemon, W. S.: Clinical manifestations of coccidioidal granuloma, *Proc. Staff Meet. Mayo Clin.* 1929, 4:305.

⁶³ Ophüls, W.: Discussion of paper by Pulford and Larson, *J.A.M.A.* 1929, 93:1049.

⁶⁴ Pulford, D. S., and Larson, E. E.: Coccidioidal granuloma; case treated by intravenous dye, colloidal lead, and colloidal copper with autopsy observations, *J.A.M.A.* 1929, 93:1049-1055.

⁶⁵ Ragle, H. E.: Coccidioidal granuloma with report of case, *U. S. Nav. M. Bull.* 1929, 27:657-661.

⁶⁶ Stockton, A. B.: Coccidioidal granuloma, treatment with thymol, case, *California & West. Med.* 1929, 31:278-280.

1930

⁶⁷ Clipman, E. D., and Templeton, H. J.: Coccidioidal granuloma, *Arch. Dermat. & Syph.* 1930, 21:259-278.

⁶⁸ DaFonseca, O.: Coccidioides immitis and coccidioidal granuloma, *Seuchenbekämpfung* 1930, 7:237-250.

⁶⁹ DeAlmeida, F.: Comparative study of coccidioidal granuloma in United States and Brazil, establishing new genus for Brazilian parasite, *Ann. Fac. de med. de Sao Paulo*, 1930, 5:125-141.

⁷⁰ DeAlmeida, F.: Differential features of etiologic agent of coccidioidal granuloma of U.S.A. and that

of Brazil, *Compt. rend. Soc. de biol.* 1930, 105:315-316.

⁷¹ Haberfelt, W.: Atypical sporocytosis of the lymph glands (blastomycosis), *Arch. f. Schiffs- u. Tropen-Hyg.* 1930, 34:549-554.

⁷² Hirsch, E. E., and D'Andrea, D.: Allergic testis reactions in guinea pigs with coccidioidal granuloma, *J. Immunol.* 1930, 18:121-125.

⁷³ Jacobson, H. P.: Coccidioidal granuloma, clinical and experimental review with report of cases, *Arch. Dermat. & Syph.* 1930, 21:790-817.

⁷⁴ Jaffé, R. M.: Microscopic changes in coccidioidal granuloma, *Virchows Arch. f. path. Anat.* 1930, 278:42-61.

⁷⁵ Kurotchkin, T. J., and Lim, C. E.: Anaphylaxis with water soluble specific substance from yeast-like fungi, *Proc. Soc. Exper. Biol. & Med.* 1930, 28:223.

⁷⁶ MacLeod, J. M. H.: Mycosis due to yeast-like fungi, *Brit. M. J.* 1930, 1:1119-1123.

⁷⁷ Pulford, D. S.: Coccidioidal granuloma, *Tr. A. Res. & Ex-Res. Physicians, Mayo Clin.* 1930, 10:94-100.

⁷⁸ Radaelli, P.: Biology of Coccidioides immitis and its systematic position, *Boll. d. Soc. ital. di biol. sper.* 1930, 5:752-756.

⁷⁹ Rand, C. W.: Coccidioidal granuloma; 2 cases simulating tumor of spinal cord, *Arch. Neurol. & Psychiat.* 1930, 25:502-511.

⁸⁰ Timpano, M.: Experiments in coccidioidal granuloma and its agent Coccidioides immitis, *Boll. d. Soc. med.-chir. di Pavia*, 1930, 44:679-722.

1931

⁸¹ Beck, M. D., Traum, J., and Harrington, E. S.: Coccidioidal granuloma, occurrence in animals, reference to skin tests, *J. Am. Vet. M. A.* 1931, 78:490-499.

⁸² Carter, R. A.: Coccidioidal granuloma, roentgen diagnosis, *Am. J. Roentgenol.* 1931, 25:715-738.

⁸³ Chou, C. H., and Reiss, F.: Coccidioidal endophthalmitis, *Nat. M. J. China*, 1931, 17:747-754.

⁸⁴ Dickson, E. C., and Beck, M. D.: Coccidioidal granuloma, *California Dept. of Public Health, Special Bull. No. 57*, 1931.

1932

⁸⁵ Ball, H. A.: Healing of coccidioidal granuloma lesion following medicinal therapy, *J.A.M.A.* 1932, 98:2279-2280.

⁸⁶ Basgal, W.: Pulmonary coccidioidal granuloma, *Rev. de path. comparée* 1932, 32:273-299.

⁸⁷ Bruhns, C.: Übersicht über die neuen Ergebnisse und Fortschritte auf dem Gebiete der Mykologie, *Zentralbl. f. Haut- u. Geschlechtskr.* 1932, 41:1-27.

⁸⁸ Caldwell, G. T.: Coccidioidal granuloma, 3 cases recognized in Texas, *Texas State J. M.* 1932, 23:327-333.

⁸⁹ Childrey, J. H., and Gray, P. A.: Coccidioidal

granuloma, primary in nasopharynx, case, California & West. Med. 1932, 37:250-252.

⁹⁰ Cicero, R. E.: Coccidioidal granuloma, case, Gac. med. de Mexico 1932, 63:139-157.

⁹¹ Davis, R. G.: Coccidioidal granuloma, case, U. S. Nav. M. Bull. 1932, 30:519-522.

⁹² DeAlmeida, F. P.: Morphology of Coccidioides immitis in tissues, Ann. Fac. de med. de Sao Paulo 1932, 7:117-123.

⁹³ DeAlmeida, F. P.: Identity of Coccidioides immitis and Pseudococcidioides mazzai, Ann. Fac. de med. de Sao Paulo 1932, 8:83-91.

⁹⁴ Montgomery, D. W.: Historical position of Coccidioides immitis among pathogenic fungi of skin, Ann. M. Hist. 1932, 4:199-202.

⁹⁵ Moore, M.: Coccidioidal granuloma; a classification of the causative agent, Coccidioides immitis, Ann. Missouri Bot. Garden, 1932, 19:397-428.

⁹⁶ Penna de Azevedo, A.: Meningeal plaques found at autopsies of cases of blastomycosis caused by Coccidioides immitis, Compt. rend. Soc. de biol. 1932, 109:125-128.

⁹⁷ Perrin, T. G.: Coccidioidal granulomatosis, demonstration of Coccidioides immitis, Gac. med. de Mexico 1932, 65:158-161.

⁹⁸ Rixford, E.: Coccidioidal granuloma, Proc. Staff Meet. Mayo Clin. 1932, 7:352-355.

⁹⁹ Stewart, R. A., and Meyer, K. F.: Isolation of Coccidioides immitis Stiles from soil, Proc. Soc. Exper. Biol. & Med. 1932, 29:937-938.

¹⁰⁰ Williams, H. B.: Non-tuberculous lung diseases, case, M. Bull. Vet. Admin. 1932, 8:435-441.

¹⁰¹ Zeisler, E. P.: Chronic coccidioidal dermatitis, unusual case, Arch. Dermat. & Syph. 1932, 25:52-71.

1933

¹⁰² Boyers, L. M.: Therapy in 2 cases of infection with Coccidioides fungus, apparently effective use of creosote and guaiacol, M. Herald 1933, 52:61-67.

¹⁰³ Imerman, S. W., and Imerman, C. P.: Coccidioidal granuloma, primary cutaneous lesion, treatment with actual cautery, Southwest. Med. 1933, 17:18-21.

¹⁰⁴ Kawatsure, S.: Animal experiments with causative agents of so-called American blastomycosis (Scopulariopsis americana, Aleurisma tularensis, and Coccidioides immitis), Arch. f. Dermat. u. Syph. 1933, 169:173-199.

¹⁰⁵ Ota, M., and Kawatsure, S.: Zur Aetiologie der echten und falschen Blastomykosen, besonders der Gilchristischen Krankheit, Arch. f. Dermat. u. Syph. 1933, 169:149.

¹⁰⁶ Reaver, D. C., and Furrer, E. D.: Pathogenic yeasts and yeast-like organisms, report of case in Minnesota simulating coccidioidal granuloma, J. Lab. & Clin. Med. 1933, 18:329-348.

¹⁰⁷ Smith, L. M.: Coccidioidal granuloma, case originating in West Texas, Arch. Dermat. & Syph. 1933, 28:175-181.

¹⁰⁸ Takahashi, S.: Experimental infection with

Coccidioides immitis, Arch. f. Dermat. u. Syph. 1933, 168:597-610.

¹⁰⁹ Walsh, G.: Yeast infections; coccidioidal granuloma, J. M. A. Alabama 1933, 2:434-437.

1934

¹¹⁰ Benham, R. W.: Fungi of blastomycosis and coccidioidal granuloma, Arch. Dermat. & Syph. 1934, 30:385-400.

¹¹¹ Carter, R. A.: Infectious granulomas of bones and joints with special reference to coccidioidal granuloma, Radiol. 1934, 23:1-16.

¹¹² Castellani, A., and Jacono, I.: Unusual forms and aspects of Coccidioides immitis in vivo, Ann. de med. nav. e colon. 1934, 40:625-634.

¹¹³ Ciferri, R., and Radaelli, P.: Phenomena of conjugation and endosporulation in vitro in Coccidioides immitis Stiles, Boll. Soc. ital. Biol. sper. 1934, 9:602-604.

¹¹⁴ Ciferri, R., and Radaelli, P.: La vita saprofittica del fungo e ex il suo potere ammonizzante, Boll. Soc. ital. Biol. sper. 1934, 9:746-748.

¹¹⁵ Ciferri, R., and Radaelli, P.: Systematic position of Coccidioides immitis Stiles, Soc. internaz. de microbiol., Boll. d. sez. ital. 1934, 6:373-376.

¹¹⁶ DeAlmeida, F. P.: Further proof of identity of Coccidioides immitis and Pseudococcidioides mazzai, Ann. Fac. de med. da Univ. de S. Paulo 1934, 10:29-32.

¹¹⁷ DeAlmeida, F. P.: Formacoes radiadas da membrana dos cogumelos parasitos, Ann. Fac. de med. da Univ. de S. Paulo 1934, 10:163-174.

¹¹⁸ Lutz, A.: Coccidioidal infection in oral mucosa, first case observed in South America, history of hypoblastomycosis americana, Mem. Inst. Oswaldo Cruz 1934, 28:585-601.

¹¹⁹ McDonald, C.: Coccidioides immitis, J. Lab. & Clin. Med. 1934, 20:47-53.

¹²⁰ Penna de Azevedo, A.: Blastomycosis of suprarenal gland due to Coccidioides immitis without lymphatic lesions and with foci of fibrosis in lungs, Mem. Inst. Oswaldo Cruz 1934, 29:189-193.

¹²¹ Radaelli, P., and Ciferri, R.: Studies on Coccidioides immitis; presence of coccidioidal granuloma in Europe, Soc. internaz. di microbiol., Boll. d. sez. ital. 1934, 6:255-257.

¹²² Ragle, H. E.: Coccidioidal granuloma, Tr. Hawaii Terr. M. A. 1934, No. 44, pp. 47-50.

¹²³ Smith, L., and Waite, W. W.: Coccidioidal granuloma, fatal case, Southwest. Med. 1934, 18:305.

¹²⁴ Stowe, W. P.: Simple technic for finding Coccidioides immitis, J. Lab. & Clin. Med. 1934, 19:1013.

¹²⁵ Tomlinson, C. C., and Bancroft, P.: Granuloma coccidioides; further observations on use of antimony and potassium tartrate and roentgen rays in treatment; additional case, J.A.M.A. 1934, 102:36-38.

1935

¹²⁶ DeAlmeida, F. P.: Consideracoes en torno dos

agentes etiologicos das blastomycoses, Ann. paulist. de med. e cir. 1935, 29:11-30.

¹²⁷ Fennel, E. A.: Coccidioidal granuloma in Hawaii, Proc. Clin. Honolulu 1935, 1:1-6.

¹²⁸ Lehman, C. F., and Pipkin, J. L.: Coccidioidal granuloma (chronic, hypertrophic), Arch. Dermat. & Syph. 1935, 31:587.

¹²⁹ Sorsky, E. D., and Nixon, C. E.: Coccidioidal granuloma with report of 18 cases with two apparent cures, California & West. Med. 1935, 42:98-106.

1936

¹³⁰ Abbott, K. H., and Cutler, O. I.: Chronic coccidioidal meningitis; review of literature and report of seven cases, Arch. Path. 1936, 21:320-330.

¹³¹ Courville, C. B.: Primary chronic coccidioidal meningitis; case with extensive subarachnoid infiltration at base of brain and about spinal cord, Bull. Los Angeles Neurol. Soc. 1936, 1:116-119.

¹³² DeAlmeida, F. P.: Cardiac inoculation of *Coccidioides immitis*, Folia clin. et biol. 1936, 8:67-69.

¹³³ Duckett, T. G., and Fredeen, R. C.: Coccidioidal granuloma, J. Kansas M. Soc. 1936, 37:111-114.

¹³⁴ Jordon, J. W., and Weidman, F. D.: Blastomycosis and coccidioidal granuloma; comparison of North and South American diseases with special reference to *Paracoccidioides brasiliensis*, Arch. Dermat. & Syph. 1936, 33:31-47.

¹³⁵ Langeron, M.: Dermatitis from coccidioides, Norw. prat. dermat. (Darier, Sabouraud, et al) 1936, 2:457-484.

¹³⁶ Sox, H. C., and Dickson, E. C.: Experimental therapy in coccidioidal granuloma, J.A.M.A. 1936, 106:777-779.

¹³⁷ Van Cleve, J. V.: Coccidioidal granuloma, J. Kansas M. Soc. 1936, 37:54.

¹³⁸ Whalen, E. J.: Pathogenic fungi, Arch. Otolaryng. 1936, 24:436-454.

1937

¹³⁹ Coccidioidal granuloma in California in 1934-1935, California & West. Med. 1937, 46:282.

¹⁴⁰ Dickson, E. C.: "Valley fever" of San Joaquin Valley and fungus coccidioides, California & West. Med. 1937, 47:151-155.

¹⁴¹ Dickson, E. C.: Coccidioides infection, Arch. Int. Med. 1937, 59:1029.

¹⁴² Gifford, M. A., Buss, W. C., Douds, R. T.: Kern County (Calif.) Health Dept. Reports, July 1, 1936, to June 30, 1937.

¹⁴³ Kehoe, E. J.: Coccidioidal infections of lung, M. Bull. Vet. Admin. 1937, 13:243-246.

¹⁴⁴ Miller, F. P.: Pulmonary manifestations of coccidioidal granuloma, Dis. of Chest 1937, 3:21-24.

¹⁴⁵ Zelman, J.: Disseminated coccidioidal granuloma (case), California & West. Med. 1937, 47:327-329.

1938

¹⁴⁶ Courville, C. B., and Abbott, K. H.: Pathology

of coccidioidal granuloma of central nervous system and its envelopes, Bull. Los Angeles Neurol. Soc. 1938, 3:27-41.

¹⁴⁷ Dickson, E. C.: Primary coccidioidomycosis, J.A.M.A. 1938, 111:1362-1365.

¹⁴⁸ Dickson, E. C., and Gifford, M. A.: Coccidioidomycosis, primary type of infection, Arch. Int. Med. 1938, 62:853-871.

¹⁴⁹ Epstein, E.: Prognostic significance of cutaneous lesions in coccidioidal granuloma, Arch. Dermat. & Syph. 1938, 38:752-755.

¹⁵⁰ Gifford, M. A.: Coccidioidomycosis, Appendix, Kern County (Calif.) Dept. of Public Health Annual Report 1938-39.

¹⁵¹ Hurwitz, S., Young, J. E., and Eddie, B. U.: Coccidioides immitis intradermal skin reaction, preliminary report of 449 cases, California & West. Med. 1938, 48:87-89.

¹⁵² Lack, A. R.: Spherule formation and endosporulation of fungus coccidioides in vitro, Proc. Soc. Exper. Biol. & Med. 1938, 38:907-909.

¹⁵³ Moore, M.: Blastomycosis, coccidioidal granuloma, and para-coccidioidal granuloma; comparative study of North American, South American, and European organisms and clinical types, Arch. Dermat. & Syph. 1938, 38:163-190.

¹⁵⁴ Nino, F. L.: Microscopic aspects of so-called blastomycotic granuloma, Prensa med. argent. 1938, 25:2203-2214.

¹⁵⁵ Stewart, R. A., and Meyer, K. F.: Metabolism of Coccidioides immitis (Stiles), J. Infect. Dis. 1938, 63:196-205.

¹⁵⁶ Wooly, M. T.: Finding of fungi in sputum, J. Lab. & Clin. Med. 1938, 23:553-565.

1939

¹⁵⁷ Brown, O. H.: Coccidioidomycosis infection in Arizona; allergic factors in nodules, Southwest. Med. 1939, 23:131-132.

¹⁵⁸ Cox, A. J., and Smith, C. E.: Arrested pulmonary coccidioidal granuloma, Arch. Path. 1939, 27:717-734.

¹⁵⁹ Faber, H. K., Smith, C. E., and Dickson, E. C.: Acute coccidioidomycosis with erythema nodosum (San Joaquin fever) in children, J. Pediat. 1939, 15:163-171.

¹⁶⁰ Farness, O. J., and Mills, C. W.: Primary infection with coccidioides in lung with cavity formation and healing, case, Am. Rev. Tuberc. 1939, 39:266-273.

¹⁶¹ Gifford, M. A.: Coccidioidomycosis, Kern County (Calif.), Session on Fungus Infection, Sixth Pacific Science Congress of the Pacific Science Assn., Aug. 1939.

¹⁶² Hynes, K. E.: Coccidioidal granuloma (2 cases, 1 treated with sulfanilamide), Northwest. Med. 1939, 38:19-21.

¹⁶³ Jacobson, H. P.: Immunotherapy for coccidi-

oidal granuloma, cases, *Arch. Dermat. & Syph.* 1939, 40:521-540.

¹⁶⁴ Kessel, J. F.: Coccidioidin skin test, *Am. J. Trop. Med.* 1939, 19:199-204.

¹⁶⁵ McMaster, P. E., and Gilfillan, C.: Coccidioid osteomyelitis, *J.A.M.A.* 1939, 112:1233-1237.

¹⁶⁶ Phillips, E. W.: Presence of coccidioid infection in Phoenix, *Southwest. Med.* 1939, 23:48-51.

¹⁶⁷ Ruddock, J. C., and Hope, R. B.: Coccidioid peritonitis, diagnosed by peritoneoscopy, *J.A.M.A.* 1939, 113:2054-2055.

¹⁶⁸ Storts, B. P.: Coccidioid granuloma simulating brain tumor in child of four years, *J.A.M.A.* 1939, 112:1334-1335.

¹⁶⁹ Thorner, J. E.: Erythema nodosum in childhood associated with infection by *Oidium coccidioides* (7 cases), *Arch. Pediat.* 1939, 56:628-638.

1940

¹⁷⁰ Cronkite, A. E., and Lack, A. R.: Primary pulmonary coccidioidomycosis, experimental infection with *Coccidioides immitis*, *J. Exper. Med.* 1940, 72:167-174.

¹⁷¹ Foley, M. P., et al: Coccidioid granuloma; report of case originating in Texas, *West. J. Surg.* 1940, 48:738-741.

¹⁷² Henrici, A. T.: Characteristics of fungus disease, *J. Bacteriol.* 1940, 39:113.

¹⁷³ Mills, C. W., and Farness, O. J.: *Coccidioides immitis* infection in Southern Arizona, *Tr. Am. Climat. & Clin. A.* 1940, 56:147.

¹⁷⁴ Moore, M.: The diagnosis of the common fungus diseases of the lung, *Am. Acad. Tuberc. Phys.* 1940, No. 10.

¹⁷⁵ Smith, C. E.: Epidemiology of acute coccidioidomycosis with erythema nodosum (San Joaquin or valley fever), *Am. J. Pub. Health* 1940, 30:600-611.

¹⁷⁶ Stewart, R. A., and Kimura, F.: Skin test for coccidioid infection; preparation and standardization of coccidioidin, *J. Infect. Dis.* 1940, 66:212-217.

¹⁷⁷ Yegian, D., and Kegel, P.: *Coccidioides immitis* infection of lung; case resembling chronic pulmonary tuberculosis, *Am. Rev. Tuberc.* 1940, 41:393-397.

1941

¹⁷⁸ Craig, W. M., and Dockerty, M. B.: Coccidioid granuloma; brief review with report of case of meningeal involvement, *Minnesota Med.* 1941, 24:150-154.

¹⁷⁹ Farness, O. J.: Coccidioidomycosis, *J.A.M.A.* 1941, 116:1749-1752.

¹⁸⁰ Kessel, J. F.: Recent observations in coccidioidomycosis, *Am. J. Trop. Med.* 1941, 21:447-453.

¹⁸¹ Powers, R. A., and Starks, D. J.: Acute (primary) coccidioidomycosis; roentgen findings in group "epidemic," *Radiol.* 1941, 37:448-453.

¹⁸² Smith, C. E., and Baker, E. E.: A summary of present status of coccidioid infection, *Weekly Bull.*

California State Dept. of Public Health 1941, 20:113.

¹⁸³ Smith, L. M.: Diagnosis of blastomycosis-like infections, *J.A.M.A.* 1941, 116:200-204.

¹⁸⁴ Thorner, J. E.: Coccidioidomycosis; relative values of coccidioidin and tuberculin testing among children of San Joaquin Valley, California & West. Med. 1941, 54:112-115.

¹⁸⁵ Winn, W. A.: Coccidioidomycosis associated with pulmonary cavitation, *Arch. Int. Med.* 1941, 68:1179-1214.

1942

¹⁸⁶ Aronson, J. D., and Gallagher, J. R.: Sensitivity to coccidioidin (as explanation of pulmonary calcification among boys in Eastern preparatory school), *Am. J. Pub. Health* 1942, 32:636-639.

¹⁸⁷ Aronson, J. D., Saylor, R. M., and Parr, E. I.: Relationship of coccidioidomycosis to calcified pulmonary nodules (in Indian children with negative tuberculin reactions), *Arch. Path.* 1942, 34:31-48.

¹⁸⁸ Ashburn, L. L., and Emmons, C. W.: Spontaneous coccidioid granuloma in lungs of wild rodents, *Arch. Path.* 1942, 34:791-800.

¹⁸⁹ Baker, E. E., and Smith, C. E.: Utilization of carbon and nitrogen compounds by *Coccidioides immitis* (Rixford and Gilchrist 1896), *J. Infect. Dis.* 1942, 70:51.

¹⁹⁰ Benninghoven, C. D., and Miller, E. R.: Coccidioidomycosis in bone, *Radiol.* 1942, 38:663-666.

¹⁹¹ Caldwell, G. T.: Secondary (granulomatous) coccidioidomycosis; coccidioid granuloma, *Texas State J. M.* 1942, 38:376-382.

¹⁹² Carter, R. A.: Coccidioidomycosis, diagnosis of fungus infections of lungs, *Radiol.* 1942, 38:649-659.

¹⁹³ Davis, B. L., Jr., Smith, R. T., and Smith, C. E.: Epidemic coccidioidomycosis, *J.A.M.A.* 1942, 118:1182-1186.

¹⁹⁴ Emmons, C. W.: Coccidioidomycosis, *Mycologia* 1942, 34:452.

¹⁹⁵ Emmons, C. W.: Isolation of *coccidioides* from soil and rodents, *Pub. Health Rep.* 1942, 57:109-111.

¹⁹⁶ Emmons, C. W., and Ashburn, L. L.: Isolation of *Haplosporangium parvum*, non-sporulating, and *Coccidioides immitis* from wild rodents; their relationship to coccidioidomycosis, *Pub. Health Rep.* 1942, 57:1715-1727.

¹⁹⁷ Kerley, P.: Significance of radiologic manifestations (in chest) of erythema nodosum (relation to sarcoidosis and coccidioidomycosis), *Brit. J. Radiol.* 1942, 15:155-165.

¹⁹⁸ Martin, C. L.: Coccidioidomycosis, roentgen-ray findings, *Texas State J. M.* 1942, 38:385-389.

¹⁹⁹ Peers, R. A., Holman, E., and Smith, C. E.: Coccidioid pulmonary disease, *Am. Rev. Tuberc.* 1942, 45:723-740.

²⁰⁰ Rosenberg, E. F., Dockerty, M. B., and Meyerding, H. W.: Coccidioid arthritis; report of case with ankle involvement and no results with sulfanil-

amide and roentgen therapy, Arch. Int. Med. 1942, 69:238-250.

²⁰¹ Schenken, J. R., and Palik, E. E.: Coccidioidomycosis in states other than California, with report of case in Louisiana, Arch. Path. 1942, 34:484-494.

²⁰² Schulze, V. E.: Acute coccidioidomycosis in western Texas, Texas State J. M., 1942, 38:372-376.

²⁰³ Shelton, R. M.: Survey of coccidioidomycosis at Camp Roberts, California, J.A.M.A. 1942, 118:1186-1190.

²⁰⁴ Smith, C. E.: Coccidioidomycosis; parallelism of the infections, Radiol. 1942, 38:643-648.

²⁰⁵ Smith, L. M.: Coccidioidal granuloma in Texas; report of 5 cases with dermatological manifestations, Texas State J. M. 1942, 38:383-385.

²⁰⁶ Stiles, G. W., and Davis, C. L.: Coccidioidal granuloma (coccidioidomycosis); incidence in man and animals; diagnosis in animals, J.A.M.A. 1942, 119:765-769.

²⁰⁷ Tager, M., and Liebow, A. A.: Intranasal and intraperitoneal infection of mouse with *Coccidioides immitis*, Yale J. Biol. & Med. 1942, 15:41-59.

²⁰⁸ Winn, W. A.: Treatment of pulmonary cavitation due to coccidioidal infection, California & West. Med. 1942, 57:45-47.

²⁰⁹ Winn, W. A., and Johnson, G. H.: Primary coccidioidomycosis; roentgenographic study of 40 cases, Ann. Int. Med. 1942, 17:407-422.

1943

²¹⁰ Baker, E. E., Mrak, E. M., and Smith, C. E.: The morphology, taxonomy, and distribution of *Coccidioides immitis* (Rixford and Gilchrist 1896), Farlowia 1943, 1:199.

²¹¹ Bush, J. D.: Coccidioidomycosis, J. M. A. Alabama 1943, 13:159-166.

²¹² Emmons, C. W.: Coccidioidomycosis in wild rodents; method of determining extent of endemic areas, Pub. Health Rep. 1943, 58:1-5.

²¹³ Goldstein, D. M., and Louie, S.: Primary pulmonary coccidioidomycosis; epidemic of 75 cases, War Med. 1943, 4:299-317.

²¹⁴ Hassid, W. J., Baker, E. E., and McCready, R. M.: Immunologically active polysaccharide produced by *Coccidioides immitis*, Rixford and Gilchrist, J. Biol. Chem. 1943, 149:303-311.

²¹⁵ Lindsay, H. C. L.: Acute coccidioidomycosis (valley or desert fever), Urol. & Cutan. Rev. 1943, 47:692-694.

²¹⁶ McDougall, T. G., and Kleinman, A. H.: Prostatitis due to *Coccidioides immitis*, J. Urol. 1943, 49:472-477.

²¹⁷ Smith, C. E.: Coccidioidomycosis, M. Clin. North America, 1943, 27:790-807.

1944

²¹⁸ Cheney, G., and Denenholz, E. J.: Diagnosis and treatment of chronic coccidioidomycosis, Arch. Int. Med. 1944, 74:311-330.

²¹⁹ Coccidioidomycosis, report of, study in the

year 1943-1944 for the Commission on Epidemiological Survey, Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army Preventive Medicine Division, Office of the Surgeon General, Service of Supply, War Department.

²²⁰ Colburn, J. R.: Roentgenologic types of pulmonary lesions in primary coccidioidomycosis, Am. J. Roentgenol. 1944, 51:1-8.

²²¹ Culliner, N. W.: Clinical aspects of coccidioidomycosis, Bull. N. E. Med. Center 1944, 6:238-242.

²²² Goldstein, D. M., and McDonald, J. B.: Primary coccidioidomycosis, pulmonary (follow-up of 75 cases with 10 more cases from new endemic area), J.A.M.A. 1944, 124:557-561.

²²³ Lee, R. V., Nixon, N., and Jamison, H. W.: Syllabus on coccidioidomycosis, Coccidioidomycosis Control Program for the AAF WFTC, 2nd ed. 1944 (unpublished but issued by the Surgeon, AAF WFTC, Hq., Santa Ana, Calif.).

²²⁴ Lee, R. V.: Coccidioidomycosis in Western Flying Training Command, California & West. Med. 1944, 61:133-134.

²²⁵ Lindsay, H. C. L.: Coccidioidomycosis involving brain, history of case, Urol. & Cutan. Rev. 1944, 48:275-278.

²²⁶ McKenney, F. D., Traum, J., and Bonestell, A. E.: Acute coccidioidomycosis in mountain gorilla (*Gorilla beringeri*) with anatomic notes, J. Am. Vet. M. A. 1944, 104:136-140.

²²⁷ Marcuse, P., and Karotkin, L.: Review of coccidioidal granuloma in Texas case, Texas State J. M. 1944, 39:534-537.

²²⁸ Michael, P., McLaughlin, R. F., and Cenac, P. L.: Unsuccessful treatment of coccidioidomycosis with penicillin, U. S. Nav. M. Bull. 1944, 43:122-124.

²²⁹ Quill, L. M., and Burch, J. C.: Surgical manifestations of coccidioidomycosis, Ann. Surg. 1944, 120:670-679.

1945

²³⁰ Ashburn, L. L., and Emmons, C. W.: Experimental Haplosporangium infection (relation to coccidioidomycosis), Arch. Path. 1945, 39:3-8.

²³¹ Bass, H. E.: Coccidioidomycosis and tuberculosis, diagnostic problem, Tuberculology 1945, 7:72-75.

²³² Cheney, G., and Denenholz, E. J.: Coccidioidin skin test, MILITARY SURGEON 1945, 96:148-156.

²³³ Christie, A., and Peterson, J. C.: Pulmonary calcification in negative reactors to tuberculin, Am. J. Pub. Health 1945, 35:1131.

²³⁴ Kunstader, R. H., and Pendergrass, R. C.: Primary coccidioidomycosis; possible pediatric problem, J.A.M.A. 1945, 127:624-627.

²³⁵ McCracken, J. P.: Coccidioidomycosis, North Carolina M. J. 1945, 6:25-31.

²³⁶ Schlumberger, H. G.: A fatal case of cerebral coccidioidomycosis with cultural studies, Am. J. M. Sc. 1945, 209:483.

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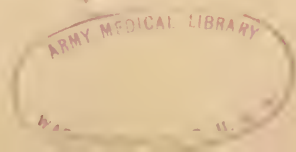
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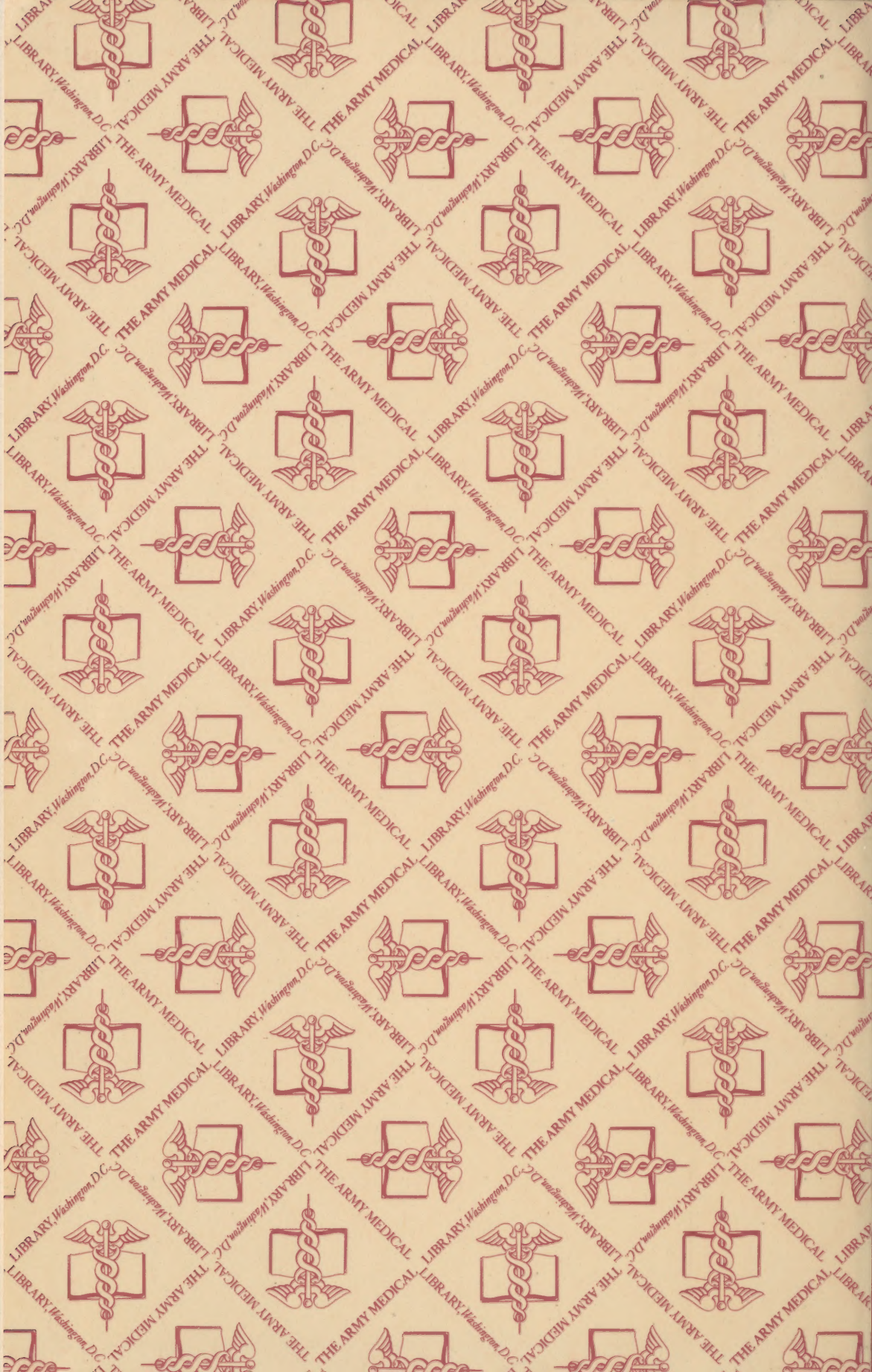
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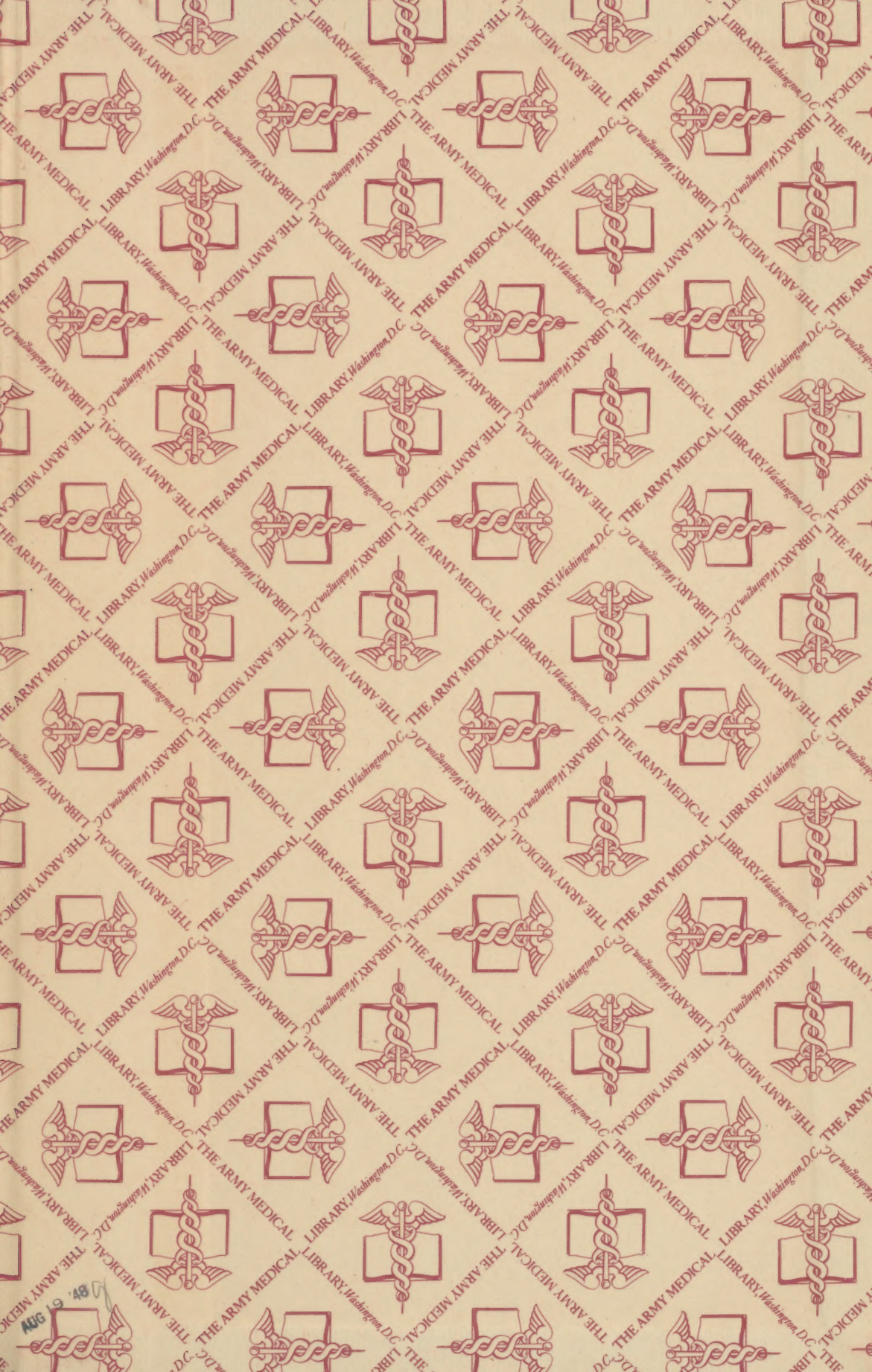
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